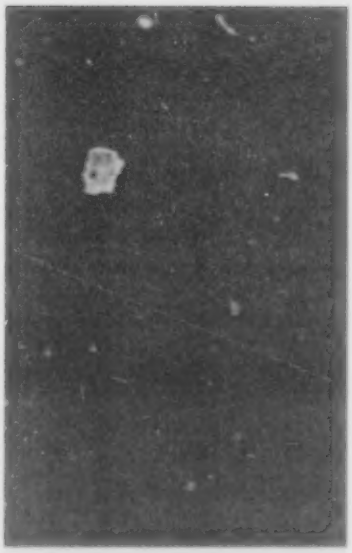

Addiction and Medications

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AADAC Alberta Alcohol and Drug Abuse Commission
An Agency of the Government of Alberta

INFORMATION SERVICES

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Acknowledgements and disclaimer

This document represents the third revision of a previous report on the same topic. All sections have been revised and updated, and some additional sections have been added. I have also taken this opportunity to correct some errors of grammar, spelling and occasionally of fact which existed in previous forms of this report. Again, I would like to thank the Alberta Alcohol and Drug Abuse Commission, and particularly Ms. Darlene James, for facilitating the preparation of this document, both by supplying me with some most valuable local information and by prompting questions or areas for discussion. I am also very grateful to Ms Cathy McCann from the College of Physicians and Surgeons of Alberta for her revision of the section on the Triplicate Prescription Program.

Views expressed in this report are those of the author. They do not necessarily coincide with the views of the Alberta Alcohol and Drug Abuse Commission.

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Summary

Addicts frequently abuse drugs that are clinically useful. In addition, addicts are sometimes treated with drugs to manage mental illness. This report deals with the pharmacology of licit drugs with some abuse liability, the drug management of diseases such as depression or schizophrenia, the possibility of interactions between drugs that affect mood and thought, populations which are at particular risk of problems, and issues such as education, advertising and legal controls.

- The extent of addiction to clinical drugs is very difficult to assess, but there is extensive use of a number of agents, particularly codeine and the benzodiazepines.
- The opioid drugs have high abuse liability, but can be used in hospitals with very little risk of addiction in the patients receiving them. An opioid which is heavily used and which may constitute a significant problem is codeine. This compound is a constituent of products such as Tylenol-3®, which are very widely used on an outpatient basis for control of pain.
- Benzodiazepines such as Valium® or Halcion® are used for the management of anxiety and insomnia, and have significant abuse liability. It is best that such agents be used for short-term treatment only, at least in the majority of patients.
- Other agents with some potential for problems include stimulants such as Ritalin® and performance-enhancing drugs such as the anabolic steroids. There are also a few non-prescription medications with some potential for abuse.
- There has been a recent upsurge of interest in the medical use of marijuana. Knowledge of the pharmacology of the drug suggests that some of these uses may be appropriate, but sound clinical evidence remains to be obtained in most areas. The mood-altering effects of the drug limit its utility in chronic conditions.
- Addicted patients may also have depression, bipolar disorder or schizophrenia. These may require long-term treatment with drugs, but the agents used have little or no abuse liability, and treatment with these medications is quite a different situation from that of drug abuse.
- Populations particularly at risk of encountering problems with drugs include young patients whose attitude to drugs is still being shaped; elderly patients and the chronically ill who take more medications; the pregnant patient whose use of drugs can affect the fetus; First Nations peoples who are at risk for a variety of reasons; and the athlete who may be tempted to use drugs to improve performance.

- Significant problems can arise from the interaction of prescribed medications. The problem becomes substantially more severe when an individual uses medications in combination with drugs taken for non-medical purposes. There is often very little information about the consequences of using combinations of different drugs in the same patient.
- Recent discoveries in neuropharmacology suggest that some medications may be useful to suppress addiction. This is still largely an experimental approach, although there are some encouraging results from studies in Europe, particularly with naltrexone and acamprosate.
- Awareness of the properties and use of medications has implications for all those who work in the addictions field.

1. Introduction

This is the third update of this report. Since 1997, when the first edition was completed, there have been significant changes in the area of the interface of substances used by addicts and those used in clinical medicine. While most of the information in previous reports is still relevant, it has been necessary to update the information, particularly with regard to the medical use of marijuana, and some new agents that have appeared in the last few years. Also, the field staff at AADAC, for whom this report is intended, have asked for some additional information. Finally, during workshops provided to AADAC, many staff members have raised concerns that fall within the areas covered by this report. This revision is thus also designed to deal with these concerns and with questions raised in the field of addition and medication.

The physician makes few distinctions between drugs used for the management of disease and drugs used for non-medical purposes. The two groups of agents are handled in a similar fashion by the body, mediate their effects through similar mechanisms, and a significant number of clinically useful drugs are also popular with addicts. It is thus entirely appropriate that AADAC, whose mandate includes addiction to licit as well as to illicit drugs, addresses the issue of the interaction of the addictive process and drugs used for disease management. This report is designed to provide some information about the problem and to suggest some possible actions to improve the situation.

1.1 Benefit and Risk

When a physician is trying to decide whether to use a particular drug in a patient, he or she will balance the possible benefits of the drug against the risks involved, because each drug is associated with a significant possibility of producing harm as well as benefit. Thus, possible addiction to a prescription drug may be one of several dangers to be put on the "risk" side of the equation. This concept is important because real benefits to the patient can occur even from the use of drugs with pronounced addiction liability. It is, of course, equally dangerous to minimize the possibility that medication for disease can be associated with addiction. The role of AADAC is to diminish the harm that can arise from the problems of addiction to any drug, but this role should be seen in the overall context of patient health.

1.2 Drugs and Addiction

Addiction is the compulsive use of drugs to the potential detriment of the addict. Addiction occurs as a consequence of the choices of the addict, and medications do not, in and of themselves, cause addiction. Addiction arises from the interaction of the personal characteristics of the user, the society in which the individual lives and the pharmacological effects of the drug on mood

and thought. Drugs produce effects that may be experienced as pleasurable, and some individuals will then continue to seek out that drug to regain the pleasure they experienced. If a drug produces no perceptible change in mood or the effects are perceived as unpleasant, as is the case with most medications, the risk of addiction is very low. Equally, when a mood-altering drug is taken appropriately for disease, the risk of addiction is also low, partly because the patient will experience the drug as therapeutic rather than recreational. This enables patients to be treated with drugs like the opioids, which addicts like to use, without usually developing an addiction.

TABLE 1: Neurotransmitters and Associated Drugs

Endorphins:	opioids (e.g., heroin, codeine, Talwin®)
Dopamine:	amphetamines, cocaine
GABA:	alcohol, sedatives
Acetylcholine:	nicotine

Serotonin is a neurotransmitter in associated pathways, but not in the reward pathway itself

As we discover more about the brain, we are starting to understand more about the addictive process. Some drugs mimic the action of naturally occurring chemicals, which transmit information from one nerve to another in "reward pathways" in the brain. These pathways provide a sensation of reward for activities, which are useful for the preservation of the individual or the species. In animals such activities include eating, drinking, sexual activity and rearing young, and these are probably also fundamental to stimulation of the reward pathway in humans. The compounds that enable nerves to communicate with each other are referred to as "neurotransmitters," and in the reward pathways, these include endorphins (dynorphin and β-endorphin), dopamine γ-aminobutyric acid (GABA) and acetylcholine. These compounds interact with structures on the next nerve in the pathway, which are called "receptors," and which serve to activate the next nerve, ultimately bringing a sensation of satisfaction. If a chemical that mimics one of these compounds is administered, it will enter the brain and stimulate the reward pathway, even in the absence of any activities that would normally stimulate this pathway. This is one of the reasons why the effects of drugs of abuse are experienced as pleasurable. In fact, because the dose of drug which can be administered is limited only by the ability of the body to tolerate it, it is possible for the user to self-administer doses of drugs which provide a stimulus in excess of that which can be achieved by normal "healthy" rewards. These drugs and the corresponding neurotransmitters are shown in Table 1.

There is now evidence that if drugs that mimic the neurotransmitters are administered repeatedly, the ability of the normal neurotransmitter to provide a sense of reward becomes suppressed. This means that the desired sensation can only be achieved by administration of the drug, often in ever-increasing amounts. For someone with a serious addiction, alternatives to drug

administration will give minimal pleasure until abstention has permitted the normal operation of that part of the brain to be restored. This goes a long way towards explaining why addiction to some agents is such a persistent problem, and why activities that provide satisfaction to someone who is not addicted, often seem to be of little significance to an addict. This is relevant to management, in that the intense drug-seeking behaviour that is observed when an addict ceases to use the drug, is due, at least in part, to the fact that repeated drug use has changed his or her fundamental neurochemical processes. The behaviour does not result merely from a lack of will power, but from something much more fundamental.

The issue is complicated by the presence of secondary pathways, which are associated with the reward pathway, and which explain, to some extent, how addiction can be seen as a learned behaviour. Unfortunately these pathways tend to be uniquely human, which makes them extremely difficult to study; the reward pathways themselves are essential to survival and seem to exist in all higher animals, but the social, cultural and personal factors, which lead to addiction or its recovery, cannot usually be studied under experimental conditions, at least not with our present technology.

1.3 Definitions

When a patient develops a craving for a drug, this is referred to as **psychological dependence**. In its mild form it is called **habituation**, and the use of tea or coffee provides an illustration. When the psychological dependence becomes more severe, we speak of **addiction**. Prolonged use of some drugs leads to a situation where the body needs the drug to function properly, and the patient will become sick or even die when the drug is stopped abruptly. This used to be called **physical dependence**, but we tend now to talk about such drugs as **producing a withdrawal syndrome** or **abstinence syndrome**. Both medical and recreational drugs can produce a withdrawal syndrome, but this has very little to do with causing or maintaining an addiction. Finally, when the individual needs increasing doses of the drug to produce the same effect, that agent is described as producing **tolerance**.

Addiction is an area which is fraught with value-laden nomenclature—consider "drug abuse" vs. "non-medical use of drugs" vs. "recreational drug use"—but it will be most useful for the purposes of this report if we define drug abuse as use of a drug where it is not needed for maintaining or improving health, and where the potential exists for adverse effects on health or behaviour.

1.4 Drug Names

Health care workers often use the **generic name** when referring to a specific drug, and an example would be diazepam. The drug may be manufactured by several different companies, each of whom will have their own **trade or brand**

name for the drug. For example, Valium® is diazepam manufactured by Roche, while Novodipam® is the same drug manufactured by Novopharm. Brand names are always followed with the symbol ®. In this document both the most popular brand name and the generic name will be used when the compound is first introduced, and the generic name thereafter. A product may contain several different compounds, in which case there will not be a single generic name that describes the drug, but there may be a single brand name. Finally if a drug becomes popular with addicts it may be given one or more **street names** by those who use it.

1.5 Prescriptions

Prescriptions provide a means of controlling medications that are potentially hazardous. In the majority of cases the hazard arises from the adverse effects of the drug in unskilled hands, and if a drug has a very low risk, it will often be available without prescription or over-the-counter. What usually occurs is that a new drug will require a prescription, and then, if there is extensive clinical evidence that the drug has few significant risks, it will be removed from the requirement for a prescription. In a few instances, non-prescription medication is kept behind the counter in the pharmacy, and the customer must specifically ask for it. In Canada, there are some drugs that are non-prescription medication at lower doses, while higher doses do require a prescription.

TABLE 2: Triplicate Prescription Drugs*

Buprenorphine
(Subutex®) (when approved) [N/A]

Butalbital with ASA, caffeine, ±codeine
(Fiorinal®, Tecnal®, Fiorinal-C®, Tecnal C®) [9,747]

Dextropropoxyphene (Darvon-N®)
[Added to list March 1, 2004]

High-potency opioids [7,502]
Alfentanil (Alfenta®)
Fentanyl (Sublimaze®)
Sufentanil (Sufenta®)

Hydrocodone (Hycodan®) [4,155]

Hydromorphone (Dilaudid®) [23,775]

Meperidine (Demerol®) [19,006]

Methylphenidate (Ritalin®) [32,382]

Methadone [6,456]

Morphine [51,092]

Oxycodone (Percodan®, Percocet® Oxy-Contin®) [138,235]

Pentazocine (Talwin®) [2,097]

* *The number of prescriptions dispensed in Alberta in 2002 is shown in brackets. The total was 307,540. This number does not correspond to the sum of the numbers in brackets, because it also includes prescriptions for drugs that are no longer monitored by the TPP.*

In Alberta, prescriptions may be written by generic or brand name. If the pharmacist receives a prescription that contains the generic name of the drug, or a brand name without the name of the manufacturer being added, any formulation of the same drug may be substituted. If the physician wants the patient to use a particular brand of a drug, he must use the brand name, and follow it either with the phrase "no substitution" or with the name of the company that manufactures it.

A program called the Alberta Triplicate Prescription Program (TPP) monitors the use of drugs that have a high addiction liability. The foundation of the program is a three-part prescription form that is used when prescribing these drugs. Two parts of the form are presented to the pharmacy where, once the prescription has been dispensed, one copy is retained by the dispensing pharmacy and the other copy is forwarded to the College of Physicians and Surgeons of Alberta for entry into the TPP database. This process is designed to discourage and document prescription forgeries, control "double doctoring" in which individuals visit two physicians for the same complaint and thus receive two prescriptions, and to obtain general information about prescribing practices in this province. The TPP provides the special prescription pads, and records are kept of stolen prescription pads. If a physician is prescribing suspicious quantities of a particular drug on the list, the appropriate regulatory authority, such as the College of Physicians and Surgeons of Alberta or the Alberta Dental Association and College, can conduct investigations. Note that certain situations are exempt from the need for triplicate prescription, including active treatment hospitals, correctional institutions and homes for the disabled, provided that the drug administration is controlled. Drugs currently included on the program are shown in Table 2, together with the number of prescriptions issued in Alberta in 2002.[1]

The use of the triplicate form requires a considerable amount of extra effort, and thus a number of medications with abuse liability can be prescribed using standard rather than triplicate prescription forms. For example, codeine is not included, which means that Tylenol-3® does not require a triplicate prescription despite its widespread abuse. Similarly the benzodiazepines such as diazepam (Valium®) are not included in the list of drugs requiring a triplicate prescription.

1.6 Introduction of New Drugs

The Federal Government, through the Health Products and Food Branch of Health Canada, approves all new drugs. The research on which the decisions are made is conducted by the pharmaceutical companies or their delegates. Massive documentation is supplied to Health Canada, and is reviewed by that body. Preliminary experiments in animals can lead to the approval of the drug

[1] College of Physicians and Surgeons of Alberta. (July 2003). *Triplicate Prescription Program Annual report for 2002*. Edmonton, AB: Author.

for investigative purposes. This means the drug cannot be used in the general population but can be used in patients who are enrolled in a clinical trial of the agent. Finally, approval for general use may be granted. Health Canada also decides whether the agent should require a prescription and it is usual to err on the side of caution. Only a few very safe drugs are released from the requirement for a prescription. This does not alter the fact that agents available without prescription are potentially hazardous and may have significant addiction liability. It is tempting to say, "make every agent a prescription drug," but it is not realistic to expect people to have to get prescriptions for common analgesics like ASA (Aspirin®), antihistamines or cosmetics.

Addiction liability is considered in pre-clinical and clinical testing, but is seldom exhaustively investigated unless there is good reason. The majority of drugs do not alter mood or behaviour, and thus pose no special problems. If the drug produces a pleasant effect, or if it belongs to a class of agent where several similar compounds are known to be addicting, then more care is taken. Even so, it is unlikely that this will lead to more than a package-insert warning. For reasons already mentioned, rational clinical use of a drug carries a rather low risk of addiction, so this is not as inappropriate as it might sound.

1.7 The Scope of the Problem

It is extremely difficult to assess the impact of prescription and non-prescription medication on the addictive process. It is possible to obtain some self-reported data about drug-taking behaviours and it is also possible to record the number of prescriptions issued for different drugs through healthcare insurance claims. In general, however, neither the physician who prescribes the medication nor the patient who receives it is likely to admit to any form of abuse or addiction. Both parties will almost invariably perceive the drugs as being of unquestioned clinical value, and concerns about over-use are usually raised after the event and are difficult to substantiate.

Recent information on the prevalence of medication use in the Alberta population is not available. However, national studies conducted in the 1990s suggest that Alberta is similar to other provinces in terms of the type of prescription drugs that are used.

Client information from the Alberta Alcohol and Drug Abuse Commission (AADAC) are shown in Figures 1 and 2.[2] It should be noted that the system used to capture this information has very broad categories, and so it is not possible to separate street drug use from prescription drug use for some drug types (e.g., heroin is included with opiates, and methamphetamine would be recorded in the stimulant group). As shown in Figure 1, the highest rates for use in the last year are for opioid drugs (23%) and antidepressants (19%). Overall,

[2] AADAC Research Services. (April 2004). ASIST 2002-2003and ASIST 2003-2004, fiscal year-end summary.

there has been little change over the last two years in the proportion of AADAC clients who report using various prescription drugs.

Figure 2 shows the percentage of AADAC clients who reported medications as drugs of concern over the past year. Of all the drugs mentioned, the opiates are a concern for 10% of clients. Far fewer AADAC clients reported concerns about their use of medications when compared to alcohol or illicit drugs like cocaine. This data suggests that there may be a problem with abuse of medications that are clinically useful, but it remains uncertain whether the user obtained the drugs by prescription for an appropriate clinical use, or whether they were obtained from the illicit market. Further, the major concern may well be that of unrecognized and unreported dependence, rather than clients whose dependence has led them to seek the help of AADAC.

FIGURE 1: Drugs Used by AADAC Clients 2002-2004. Percentage of treatment clients reporting use of these classes of drugs in the past 12 months

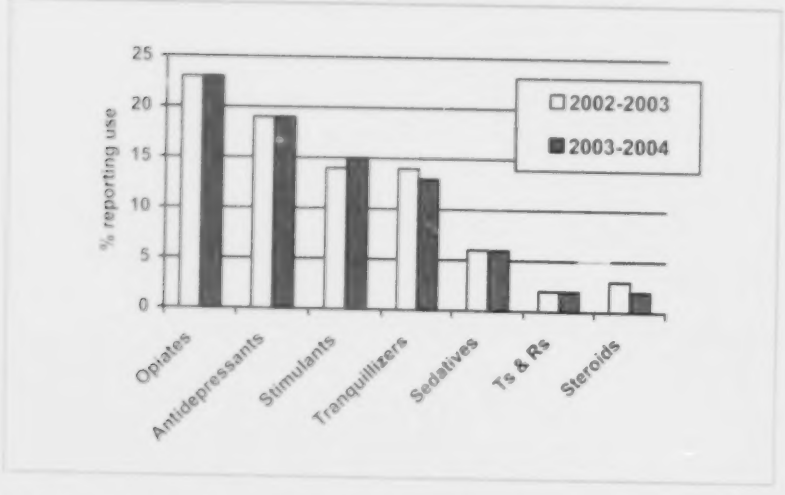
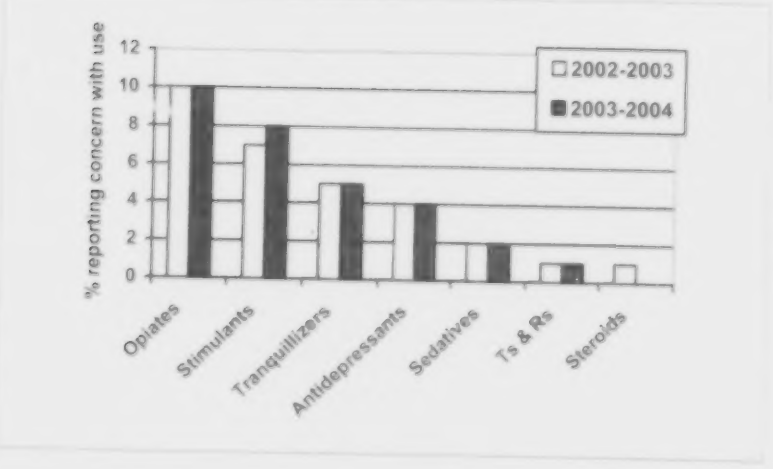


FIGURE 2: Drugs of Concern to AADAC Clients 2002-2004. Percentage of treatment clients reporting these classes as their drug of concern



The Alberta Youth Experience Survey (TAYES) showed that about 4% of students from grades 7 to 12 had used "uppers without a prescription" and 2% had used "downers without a prescription".[1] This suggests that use of prescription medication, whether shared, borrowed or stolen is relatively low in this age group.

While one way of determining the extent of the problem of medication use is to examine the number of prescriptions written (see Table 2), the issue is complicated by the variability of prescribing practice within various patient groups. For example, in a hospital setting, the use of powerful opioid drugs is much higher than in an outpatient clinic, but the extent of abuse of these compounds is negligible.

[1] AADAC (June 2003). *The Alberta Youth Experience Survey 2002: Summary report.* Edmonton, AB: Author.

2. Prescription Drugs With Abuse Liability

2.1 The Opioids

2.1.1 Overview

Opioid drugs are the most powerful analgesics known, and this forms their major clinical use. Documentation that mentions opium, the prototype material, is found in writings from as long ago as 3000 B.C. Opium is derived from a particular variety of poppy (the opium poppy or *papaver somniferum*) and it has long been recognized as a product that can relieve pain, relieve diarrhea (or produce constipation, depending on your perspective!), and provide feelings of peace and delight. Addiction to opium was common in ancient Greece and the free availability of opium-containing drugs during the nineteenth century in the United States made addiction common in that country also, where it was known as "The Soldiers Disease." At the turn of the century it was estimated that about four percent of the United States population were addicted to opium. For reasons outlined later (see Section 8, Legal Controls), it is becoming common to reserve the term **narcotic**, which was previously used to describe this group of drugs, for legal use, and to refer to the drugs related to opium as the **opiates** if they are structurally similar to the natural alkaloids, and the term **opioids** if they have similar pharmacological properties.

2.1.2 Biological Actions

The opioids are used primarily for relief of pain. Pain involves two processes: one is the awareness of discomfort, and the second is the reaction to it. Drugs like acetaminophen (Tylenol®) relieve the sensation of pain, but are devoid of psychological effects. The opioids relieve both, and are thus used for severe pain such as that encountered after surgery, or in terminal illness. In addition, these agents decrease the movement of food through the intestine, making them effective in the control of diarrhea, as well as making constipation a significant adverse effect, particularly in the elderly. The drugs can also cause nausea, and have a few other effects such as suppression of cough. There is a significant incidence of allergy to these drugs, resulting in itching or skin rash. It is important to note that patients in pain who receive the opioids do not usually get the sort of "high" which is experienced by the addict who uses the same drug, although the sensation of relief of the experience of pain and of peace which results from the use of an opioid will certainly lead to a desire to continue to obtain relief. Despite this, the large majority of those who receive these drugs in a clinical setting do not become addicted, although long-term use followed by abrupt cessation will invariably lead to an abstinence syndrome. Very recent evidence suggests that, although there has been an overall increase

in the clinical use of opioid drugs (particularly the high potency agents), the incidence of abuse of prescription opioids has remained stable.

The mechanism of action of these drugs is rather well understood, and a major discussion is beyond the scope of this review. Briefly, the drugs imitate the action of hormones that are made in the body and are called endorphins. The endorphins, our own personal opioids, are involved in a large number of processes in the brain. For example, they are released when we exercise, thus giving a physiological basis for "runners' high." When the synthetic opioid drugs are administered, they react with the body like a huge dose of endorphin. Some of the opioids are well absorbed when they are taken by mouth, but others find their way into the blood (and hence into the brain) only with difficulty, unless they are injected. This adds a significant complication, in that intravenous use of these drugs by addicts carries with it a high risk of other medical problems, including hepatitis and HIV infection.

2.1.3 Opioid Addiction

The sensations produced by these drugs are so pleasing to some individuals that the abuse liability is very high. The addict develops strong psychological dependence, and the abrupt cessation of the use of these drugs is accompanied by a significant withdrawal syndrome that includes fear, agitation, sweating, goose bumps (whose presence gives rise to the expression "cold turkey"), dilation of the pupil of the eye, vomiting, diarrhea, urinary incontinence, increased blood pressure and fever. This peaks at about three days, and then subsides. The drugs produce tolerance, and doses that may be near lethal for non-tolerant individuals merely produce an acceptable high in the addict. Once someone has withdrawn completely from the drug, the tolerance also disappears. The psychological dependence on the drug, however, may continue unabated. The phrase "narcotics hunger" has been used to describe this sensation, and if we define the success rate for "cure" of an addiction in the same way as for cancer (i.e., as five years free of disease) the rate is probably less than 10%. This is not to suggest that rehabilitation is hopeless. The medical perspective of "cure" may not correspond to the social aspects. For example, someone who remains drug-free for periods of one to two years with rare episodes of recurrent addiction has clearly gained over the untreated addict. It does, however, emphasize that it is difficult to remove the addiction totally, a fact which is well known in the treatment of alcohol and other drug abuse.

The individual who becomes addicted to opioid drugs is generally not violent, unless violence is necessary to obtain the drug. Equally, these agents do not appear to exert massive damage on the heart or blood vessels, kidneys, liver, lungs or other organs. In fact some addicts live to a ripe old age, provided that they can obtain their drug in a pure form and avoid exposing themselves to the risks associated with illicit activity. Those who die from opioid use tend to die from violent activities associated with drug dealing, from accidental overdose where the drugs reduce breathing so the patient becomes unconscious and then

asphyxiates, or from infection associated with intravenous drug use. The drugs diminish most normal motivations, so the addict is seldom ambitious or social. The drug tends to replace such things as family, sex or career as an objective for living, for reasons mentioned in Section 1.2.

2.1.4 Clinical Use of the Opioids

The opioids currently available for clinical use in Canada are shown in Table 3. These have been classified as (1) "super-potent" which are used mostly in some forms of anaesthesia, (2) "systemic analgesic" which are the mainstay of the management of moderate to severe pain, (3) "orally-active" which are effective analgesics by mouth and (4) "other" which lists some agents which are structurally related to the opioids but which lack addiction liability. This is not the usual pharmacological classification, but it will be easier to discuss the individual drugs in this context. Tramadol (Ultram®) is a weak opioid that is listed in the U.S. pharmacopoeia, but is currently unavailable in Canada. It appears to have a rather low incidence of abuse. Levorphanol (Levo-dDomoran®) and the mixed opium alkaloids (Pantopon®) are no longer listed in the Compendium of Pharmaceuticals and Specialties (CPS, see "Additional Reading"). Most of the opioids are quite similar in duration of action, lasting two to four hours, although methadone has a much longer duration of action, and some of the newer drugs that are not currently available in Canada are eliminated even more slowly.

TABLE 3: Opioids in Clinical Use

High-Potency anesthetics
- Fentanyl (Sublimaze®)
- Sufentanil (Sufenta®)
- Alfentanil (Alfenta®)
- Oxymorphone (Numorphan®)

Systemic analgesics
- Morphine (MS Contin)
- Diamorphine, heroin
- Meperidine, pethidine (Demerol®)
- Butorphanol (Stadol NS®)
- Hydromorphone (Dilaudid®)
- Nalbuphine (Nubain®)
- Methadone

Orally-active
- Codeine
- Oxycodone (Percodan®, Percocet®, OxyContin®)
- Pentazocine (Talwin®)
- Propoxyphene (Darvon®)

Other
- Hydrocodone (Hycodan®) *cough/pain relief*
- Dextromethorphan *cough*
- Loperamide (Immodium®) *diarrhea*
- Diphenoxylate (Lomotil®) *diarrhea*

The very potent opioids are rather uncommon drugs, both clinically and in addiction, although fentanyl is known to be manufactured in illicit laboratories, and has been responsible for deaths from drug overdose, chiefly in California. These drugs are many times more potent than the more familiar opioids, and, in consequence, carry with them a high risk of accidental overdose.

Morphine is the most important of the more than twenty opioids that are found in crude opium. It is absorbed orally, but poorly and unpredictably, so in a clinical setting morphine is very often used either by injection or by an intravenous drip. It is used mostly for pain relief, although acute episodes of congestion of the lungs are often treated with morphine, where it both calms the patient, and has some systemic effects that are beneficial. MS Contin is a sustained release preparation of morphine, administered either as sustained release tablets or as a sustained release suppository. Because MS Contin is a form of morphine that is available from pharmacies and is thus not contaminated with impurities, it has become a very popular substitute for heroin in some provinces, including Alberta.

Meperidine (Demerol®), called pethidine in Europe, is a synthetic opioid that has similar effects to morphine. Meperidine can produce depression (dysphoria) as often as euphoria and is less favoured by addicts, although there is still a significant street market for the drug. Meperidine is used almost entirely in pain control, and recent evidence suggests that its clinical use is decreasing. Heroin (diamorphine) is a synthetic derivative of morphine, which has the advantage, from the perspective of the addict, that it enters the brain very rapidly and thus produces a particularly dramatic onset (the "rush"). Whether heroin should be available for pain control is a difficult question. It is used in some countries because in pain relief, particularly for terminal patients, the issue of addiction is not serious. On the other hand, clinical trials have usually failed to demonstrate any advantage of heroin over morphine, and physicians fear that a legal source of heroin would create significant problems of the drug being diverted to the illicit market. The issue of prescription of heroin to opioid addicts is discussed later in this section.

An effective orally active opioid is pentazocine (Talwin®). This drug was believed for many years to be a "partial agonist" which would stimulate the opioid receptor at low doses and block it at higher doses. Ironically, pentazocine was originally believed to be non-addicting because of this property. We now know that pentazocine owes its activity to a slightly different spectrum of activity from morphine or heroin, and indeed, the nature of the drug "high" is also different. It is a weak antagonist at some opioid receptors. Pentazocine is used chiefly for outpatient management of moderate to severe pain, such as that associated with surgery, but because of its abuse liability, it is being used less frequently. In addition, it has been re-formulated (Talwin-Nx®) to make injection ineffective and potentially hazardous, making it more difficult for addicts to use. This drug is not usually favoured by those with an addiction to heroin, but it has had its own followers, particularly when combined with the stimulant methylphenidate

(Ritalin®). This combination is referred to colloquially as "Ts & Rs" or "poor man's heroin" and will be discussed in the section on stimulants.

The best known of all the opioids is probably codeine. Codeine is rather a weak pain reliever when compared with morphine, but because its mechanism of action is different from agents like acetylsalicylic acid (ASA, Aspirin®) or acetaminophen (Tylenol®), codeine can be added to these other agents to enhance pain relief. The amount of codeine that is added varies from 8 mg to 60 mg per tablet. Current regulations permit combinations containing codeine to be sold without prescription if there is no more than 8 mg of codeine in each tablet and there are at least two other ingredients. Tylenol-3® and 292®s, both of which contain 30 mg of codeine in each tablet, are excellent agents for control of temporary but moderate pain such as accompanies dental extractions. The strongest preparation, Tylenol-4®, contains 60 mg of codeine, but is used much less frequently than the weaker preparations. Another unusual but still troubling product is 282-Mep®, which contains 15 mg of codeine, but also contains 200 mg of the anti-anxiety agent, meprobamate. In addition, codeine is a constituent of cough medicines because opioids suppress cough. The extent of addiction to codeine-containing compounds is very difficult to assess because the agents are widely available for legitimate use and because they are used to treat pain, a condition that is both very frequent and difficult to measure objectively. There have been plenty of unquestioned cases of addiction to codeine, and, *in extremis*, a heroin addict may get some relief from codeine, although it will not fully replace their drug of choice.

Another weak opioid drug, which is a little more potent than codeine, but much less popular, is propoxyphene (Darvon®). This compound is also available in combination with ASA as 692® tablets. Propoxyphene has recently been placed on the Triplicate Prescription list of monitored drugs.

There are three opioids and one near-opioid that remain to be discussed. The first of these is hydrocodone (Hycodan®), which has some abuse liability, but was used almost exclusively for treating cough. More recently a combination of hydrocodone and acetaminophen has been aggressively marketed in the U.S. as Vicodin®, a pain-relieving drug. Diphenoxylate (Lomotil®) and loperamide (Immodium®) are agents that produce significant constipation. This is a property of all opioids, but is particularly evident in these drugs, which is why they are used for the symptomatic control of diarrhea. Addiction to them is rare.

Dextromethorphan is a compound that is structurally very similar to the opioids, but lacks any opioid-like properties except for suppression of cough. Clinical trials have shown dextromethorphan to be about equi-effective with codeine, but individuals may obtain more relief with one drug rather than the other. The agent does not produce a morphine-like high, but at very high doses it is an antagonist at receptors for N-methyl D-aspartate a stimulant neurotransmitter in the brain, a property that is shared by the dissociative anesthetic ketamine, which is discussed in Section 2.6. Very large doses of dextromethorphan produce a state of

dissociation accompanied by sensations of power and insight, but it also appears to have the potential to produce long-term and negative changes in thought processes. A drug-friendly website[4] recommends against its use, but there is very little good clinical information about abuse of this compound. Finally it should be pointed out that although ASA and acetaminophen are over-used, neither have any significant effects on mood and thus do not represent a significant problem in terms of real addiction.

2.1.5 Opioid Antagonists and Detoxification

Opioids that are used clinically are all agonists; that is, they provide effects that arise from stimulation of the opioid receptors, and are thus similar to the endogenous opioid transmitters. We have known for many years that some compounds have opposite effects and can block the opioid receptor and thus reverse the effects of both the endorphins and opioids taken by addicts or patients. These compounds are referred to as "antagonists." Opioid antagonists will thus prevent the effects of heroin, morphine or similar drugs, and in a patient who is experiencing the effects of an opioid. Administration of an antagonist will produce an immediate cessation of those effects, and immediate production of a full-blown withdrawal syndrome, which can be very dangerous. Even a weak antagonist, such as pentazocine, can precipitate withdrawal in someone addicted to and intoxicated with heroin. The drug naloxone (Narcan®) is used to reverse the effects of opioids in those who have had an accidental overdose of drugs in this class. It is very short acting, and must be given by repeated injection if the patient is not to suffer a return to the adverse effects of the opioid itself.

More recently, a longer-acting opioid antagonist called naltrexone (Revia®) has excited interest as an adjunctive therapy for recovering opioid addicts. The theory behind the use of this agent is that in a patient taking naltrexone, administration of opioids will have no appreciable effects, and it will thus facilitate the individual remaining drug-free. There is reason to believe that some patients are helped to a considerable extent by treatment with naltrexone. This drug is given daily and in healthy patients seems to have few adverse effects. There are, however, four important issues. First, in patients who are still abusing opioids, naltrexone produces a withdrawal syndrome, and thus a "washout" period of seven to 10 days must be observed between cessation of opioid use and administration of naltrexone. It is recommended that individuals first receive a "challenge" with naloxone, which is readily reversible, in case they have been misrepresenting their opioid use. The withdrawal syndrome will appear with naloxone, but is short lasting. The second point is that some individuals will try to experience the effects of heroin, even though they have been treated with naltrexone, by taking very large doses of morphine or heroin. This may be effective but it is very dangerous; it is much more difficult to judge the dose, and this process can easily result in death. Thirdly, naltrexone can produce severe liver damage under circumstances

[4] The Vaults of Erowid (online at: www.erowid.org).

where there is some liver damage to start with. This makes it more difficult to use in those with dependence on both alcohol and opiates, although the liver damage is only apparent at doses that are larger than those used in recovering addicts. Finally, the patient on naltrexone will not obtain good analgesia from opioid drugs unless larger doses are used, and this may result in increased depression of breathing. If opioid analgesia is needed, the management thus becomes both more complicated and more hazardous.

The use of naltrexone is probably of benefit to highly motivated individuals, and the patients who have withdrawn from the opioids tend to be calmer and more tractable if they have been treated with the drug. There is good evidence that the drug is also effective in recovering alcoholics, and this might be predicted, since alcohol works "upstream" of the opioid sites in the brain. Buprenorphine (Buprenex®) is another antagonist, but one with sufficient agonist-like activity to have the potential for abuse. It is well absorbed from a tablet held under the tongue, and recent data suggests that it may convey some additional advantages. Buprenorphine is approved and used in the U.S., but is available in Canada only with a special approval. It has been formulated with the full antagonist naloxone added to the tablet. While naloxone is not orally active and will thus not interfere with the action of buprenorphine when it is used orally, attempts by an addict to inject buprenorphine will not be successful.

In the last few years ultra-rapid opioid detoxification (UROD) has been developed. Here, the addict who is still using an opioid drug is managed medically by anaesthesia, followed by treatment with doses of narcotic antagonist, usually naltrexone, and sometimes also with clonidine (Catapres®) which deals with many of the physical effects of withdrawal. The individual thus withdraws from the opioid over a short period of time—less than 12 hours—under general anaesthesia. Often a dose of naltrexone will be given at the conclusion of the withdrawal stage, to aid the patient to abstain during the immediate post-withdrawal period. There is little doubt that the process is very much more comfortable for the addict, but so far, studies have failed to show any significant increase in long-term abstinence. UROD clinics currently exist in Vancouver and Toronto. The procedure is not covered under Medicare, and recently there have been some concerns that the procedure is not as safe as is generally claimed, with at least one death being attributable to UROD. Simply releasing a patient after UROD with a depot preparation of naltrexone without other extensive follow-up measures is not likely to be an effective way of reducing the incidence of relapse.

2.1.6 Replacement Therapy

In selected addicts, the administration of methadone under medical supervision, to substitute for heroin or other opioids, has been really helpful. Even if it does not lead ultimately to a drug-free lifestyle, it can improve the quality of life for the addict, who no longer has to resort to crime to support his habit. It also makes sense from an economic perspective, since the untreated addict requires at least $100/day to support their habit, money that is almost always obtained from

criminal activity at an overall cost to society that is enormously higher than that of operating a methadone maintenance program.

The AADAC Opiate Dependency Program (ODP) operates in Edmonton and now in Calgary; privately operated methadone clinics are also open in Red Deer and Calgary. The AADAC program stabilizes opioid-dependent clients on individualized doses of methadone administered orally, and provides additional support services. Admission to the program depends on the client demonstrating opioid dependence, with previous and unsuccessful attempts at treatment by other means. Within this program, treatment planning may include addiction counselling, or referral to other appropriate services such as employment counselling, life skills training, or educational development. Clients are encouraged to stay on methadone as long as they benefit from it. Since a full-blown withdrawal syndrome accompanies cessation of the use of methadone, the process of withdrawal from methadone is not an easy one. Clients choosing to withdraw from methadone are tapered off gradually to minimize withdrawal symptoms. AADAC operates the ODP in collaboration with community-based physicians and pharmacists, and more than 600 patients are currently registered in the program. A recent report has been prepared by the provincial Opioid Dependency Treatment Co-ordinating Committee and it provides a number of recommendations for enhancing opioid dependency services in Alberta.[5]

Other drugs have also been tried in replacement therapy. L-alpha-acetylmethadol (LAAM) is like methadone, but it is a "pro-drug" (a drug which is activated by the body) and can be given less often—once every two to three days, which is more convenient for the patient and for the clinic. A recent systematic review suggests that it is more effective than methadone in reducing the use of heroin, but also points out that it has been associated with cardiovascular complications, which may prevent its approval for general use.[6]

Buprenorphine (introduced in Section 2.1.5) is a partial agonist that is a compound that has both stimulant and antagonist activities, so the effects reach a ceiling and withdrawal is (supposedly) much easier than with methadone. At steady-state, the drug has antagonist effects and will block the action of heroin, which may discourage those in the replacement program from supplementing their treatment with illicit opioids. As mentioned previously, it is sometimes combined with naloxone, which is an antagonist that is active only if it is injected. Neither LAAM or buprenorphine are currently available for maintenance therapy in Canada, and even in the U.S., methadone is still regarded as the "gold standard" for treating persons dependent on opioid drugs.

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[5] Provincial Opiate Dependency Treatment Subcommittee of the Addiction Task Group. (February 2004). *A framework for the delivery of opioid dependency treatment in Alberta*. Edmonton, AB: Author.

[6] Clark, N., Lintzeris, N., Gijsbers, A., Whelan, G., Dunlop, A., Ritter, A. & Ling, W. LAAM maintenance vs. methadone maintenance for heroin dependence (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004, Chichester, UK: John Wiley & Sons, Ltd.

In some countries the approach taken has been even more radical. In the United Kingdom, registered opioid addicts could obtain heroin in a disposable syringe from a pharmacy at a nominal fee. Shortly after this rule was first introduced, the per capita incidence of opioid addiction in the United Kingdom was only about one tenth of that in the United States. Currently in the UK, the use of heroin replacement therapy is restricted to clinics, and illegal immigrants cannot access these clinics. As a result, a significant illicit market for heroin has developed. Nevertheless, providing heroin for addicts may have advantages; the lack of profit for the dealer, who once he had a client "hooked" would see the unfortunate addict able to continue his habit through legal channels, made dealing in opioid drugs an unprofitable business. Equally, while not all addicts are content to forego the intensity of the heroin experience and switch to methadone, most would certainly appreciate a supply of inexpensive heroin of unquestioned purity.

In Switzerland, a similar program has been introduced. The outcome of the Swiss program was originally reported as being very favourable, but the data have been pertinently criticized. It is difficult to escape the feeling, however, that the vehement criticism of this trial arose more from a distaste of the process of giving heroin to addicts than from an objective evaluation of an admittedly flawed study. A recent report from Switzerland suggests that the program is indeed successful, but points out those in the program show an increase in unemployment and reliance on social welfare. Germany, the Netherlands and Spain are considering adoption of this approach.[7, 8]

In Canada, prescription of heroin for maintenance therapy in opioid addicts is not permitted. However, a private members' bill which raised the issue for discussion and consideration by the Standing Committee on Health was introduced in 1999 by Libby Davis MP. Currently, the Canadian Institutes for Health Research has approved a multi-centre trial of heroin prescription in Toronto, Vancouver and Montreal. The trial will involve about 500 addicted patients and is referred to as the North American Opioid Maintenance Initiative (NAOMI).[9]

The motivation for attempting to diminish injection drug use by the most effective method, regardless of conventional views on the topic, has undoubtedly been spurred by the significant role of intravenous drug use in the spread of HIV, hepatitis and other severe infections.

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[7] Maag, V. (2003). Estimated trends in the prevalence of heroin addiction in Switzerland. A multiple-indicator approach. *European Addiction Research, 9*, 176-181.

[8] Brehmer, C.& Iten, P.X. (2001). Medical prescription of heroin to chronic heroin addicts in Switzerland–a review. *Forensic Science International, 21*, 23-26.

[9] Ontario Federation of Community Mental Health and Addiction Programs (online at: http://www.ofcmhap.on.ca/addiction/north_american_opiate_medication.htm).

Points to Consider

- The incidence of **illicit** addiction to intravenous heroin and other opioids is low in Alberta, at least when compared with large cities in the United States and elsewhere. In a survey conducted in 2002, less than 0.1% of the adult population were frequent users of heroin (as opposed to about 2% for amphetamines and about 12% for cannabis) although about 10% of AADAC clients list opioids as a drug of concern.[10, 11]

- Addiction to codeine-containing preparations may be more widespread and there are certainly a large number of prescriptions written for outpatient use of ASA-codeine or acetaminophen-codeine drug combinations. Drugs of this type are among the most commonly prescribed of all agents in the province. Any addiction, however, will often be unrecognized, because the user starts to take the drugs for the real clinical purpose (i.e., pain control). It becomes easy to attribute continued use not to addiction but to the continued presence of pain.

- Medically, in a hospital setting, more problems are encountered from under-use and misuse of opioids than from over-use. This arises because of fear on the part of physicians and nurses that they will create an addiction, and this sometimes causes them to withhold the drugs or use them at inadequate doses or at widely separated intervals. In fact, some studies have shown that if patients are allowed to control their own medication, they experience improved pain relief and do not use more of the drug. It is important that in an effort to reduce drug dependence we do not foster the idea that correct medical use of the opioids leads to high risks of addiction, and every effort should be made to educate physicians, particularly those dealing with chronic pain, to ensure that the best possible pain relief can be achieved.

- Long-term self-medication with codeine-containing products should be discouraged. The issue is a simple one: if someone has been using quantities of these drugs, they need to consult with a doctor. These drugs relieve pain, but they do not deal with the underlying cause. In a few instances, there may be little the doctor can do except relieve the pain. In many instances, however, there are better approaches. For example, there are a number of new agents for migraine headaches, and if someone suffering from this condition is self-medicating with agents such as 222s®, they may do better to use a different and more selective drug. Long term-use of opioids without frequent medical advice is to be strongly discouraged.

[10] Wild, T.C., Curtis, M. & Pazderka-Robinson, H. (October 2003). *Drug use in Edmonton (2001-02): A CCENDU report.* Edmonton, AB: University of Alberta, Addiction and Mental Health Research Laboratory.

[11] Ibid, note 2.

2.2 The Benzodiazepines

2.2.1 Overview

The benzodiazepines are drugs that have revolutionized the management of anxiety and insomnia. When they were first introduced they were greatly overused, and used for inappropriate reasons. They may still be overused, but everyone is becoming more aware of the problems associated with them. The best-known drug in this class is undoubtedly diazepam (Valium®), but there are many others, including the controversial drug triazolam (Halcion®). These drugs have a unique mechanism of action, and members of the benzodiazepine family are used for management of anxiety and insomnia. They are also used, less often, as muscle relaxants or in the control of seizures. A list of the available drugs will be found in Table 4, together with their major clinical applications.

2.2.2 Use in Anxiety

Anxiety is epidemic in modern society, although opinions differ as to the extent to which anxiety may be considered part of the normal fabric of life. Benzodiazepines are surprisingly non-toxic, and can be taken for years with little or no obvious damage to any organ system. In acute overdose they are rarely lethal unless combined with other drugs, but the alcohol-benzodiazepine combination is particularly dangerous. Like all other sedative-hypnotic drugs (drugs which both calm and promote sleep), the benzodiazepines have effects that are dependent both on the specific drug involved, and on the dose. In general, relief from anxiety is followed at higher doses by removal of inhibitions, followed by sleepiness and then sleep. Larger doses produce general anaesthesia, followed by coma, and if the dose is very large, by death. The benzodiazepines follow this path over a wide range of doses. Thus, the dose to produce coma is many times larger than the dose to produce relief from anxiety. This is not true of other drugs such as the barbiturates, where the separation between therapeutic and lethal doses is much less, and this contributes to the relative safety of the benzodiazepines. Unfortunately, benzodiazepines can create mental clouding, which is sometimes subtle, and may not be appreciated by the user until the administration of the drug is stopped. Benzodiazepines are taken to produce some psychological numbing, and it would be surprising indeed if all they did was to relieve anxiety without any additional psychological effects. A second issue is that it is dangerous to promote the idea that there is always a pharmacological solution to mental discomfort. While some physicians have no problems with lifelong administration of benzodiazepines for anxiety, their numbers are decreasing, and the majority of doctors now use the drug for rather short periods of time and only in selected patients. While any of the benzodiazepines have some anxiety-relieving action, those most frequently used have been listed in the first

part of Table 4. The drugs differ chiefly in their duration of action and thus in the frequency with which they must be taken. Flunitrazepam (Rohypnol®) represents a special case and is discussed in Section 2.2.5, Benzodiazepine Abuse.

2.2.3 Use in Insomnia

The use of the benzodiazepines in insomnia is at least as controversial as their use in anxiety. Insomnia is not uncommon, and is distressing for the sufferer even if it is not generally regarded as a serious condition. The benzodiazepines are sedative, and the most popular agents of this type are flurazepam (Dalmane®), temazepam (Restoril®) and triazolam (Halcion®). These agents are safer than the older hypnotic drugs, such as the barbiturates, and may produce less disturbances of the normal sleep pattern. Triazolam was widely used until recently, when its adverse effect on memory became apparent. This drug remains in the body only for a very short period of time, and thus in theory, can help people to fall asleep, and then hand over the job of keeping the person asleep to normal sleep mechanisms. This seemed to work very well, but increasing reports of confusion and memory impairment, particularly in the elderly, has caused widespread concern.

TABLE 4: Benzodiazepines in Clinical Use

Anti-anxiety

- Lorazepam (Ativan®)
- Clorazepate (Tranzene®)
- Bromazepam (Lectopam®)
- Diazepam (Valium®)
- Chlordiazepoxide (Librium®)
- Alprazolam (Xanax®)
- Oxazepam
- Flunitrazepam (Rohypnol®)(not legally available in North America)

Sleep-inducing

- Flurazepam (Dalmane®)
- Nitrazepam (Mogadon®)
- Triazolam (Halcion®)
- Temazepam (Restoril®)
- Midazolam (Versed®)

Other

- Clonazepam (Rivotril®)
- Clobazam (Frisium®)

The issue of management of insomnia by drugs is important. A strong case can be made for using these drugs only for brief periods of time and in highly selected patients, because in many instances the disturbance in sleep pattern is more imaginary than real. In addition, the insomnia may be caused by behaviours that can be changed, thus removing the necessity of providing drug therapy. Caffeine use is a frequent culprit, as are other negative lifestyle components. A particular problem with most sleep-inducing drugs, including

the benzodiazepines, is "rebound insomnia." If the drug is administered for a couple of weeks and then stopped, the first few nights of natural sleep after withdrawal of the drug will often be disturbed. Even though a satisfactory sleep pattern soon returns, it is easy for the individual to resume taking the drug to obtain the rest they need.

2.2.4 Other Clinical Uses

Benzodiazepines have been considered for many years as drugs for the management of withdrawal from alcohol. They may have some role to play in this process, but it is astoundingly easy merely to replace a dependence on alcohol with a dependence on the benzodiazepines, so considerable care is needed. These drugs are sometimes used under other circumstances. For example, clonazepam (Rivotril®) and clobazam (Frisium®) are used exclusively for their anticonvulsant effects, and diazepam is also used as a muscle relaxant.

2.2.5 Benzodiazepine Abuse

While the benzodiazepines do have some street value, they are very widely available, and the problems with dependence arise more from overuse and continued use when they are not required than from street addiction. Those who are psychologically dependent on the benzodiazepines will generally not think of themselves as addicts, but as people receiving therapeutic drugs. In normal therapeutic doses, the drugs do not produce a significant withdrawal syndrome, but in larger doses, there is a clear-cut and uncomfortable withdrawal syndrome associated with abrupt cessation of drug use. Withdrawal from prolonged use of the benzodiazepines takes some care, support and understanding.

Flunitrazepam (Rohypnol®) represents a special case. This drug is available as an anti-anxiety agent in much of Europe and some parts of Central and South America. It has never been sold in Canada or the U.S., although for some years, those with a prescription for flunitrazepam from other countries were allowed to possess the drug in the U.S. In larger doses, the drug both disinhibits and impairs memory, and this has led to the drug sometimes being a preferred drug of abuse, particularly but not exclusively in Texas. Flunitrazepam tablets are often known as "Roofies" when they are available for non-medical purposes. The drug is probably not widely abused in Canada, although persistent if anecdotal reports of its use occur. Flunitrazepam is readily soluble in water and is tasteless, and this led to it developing considerable notoriety as a "date-rape" drug. There have been reported cases of men who have secretly added this drug to their date's drink, and then taken advantage of the disinhibiting and memory-impairing effects to commit rape. The manufacturers have reformulated the agent so that the tablets are less soluble and release a blue dye when dissolved, which will certainly help. The drug remains detectable in the body only for two to three days, so it is important to get blood levels tested rapidly if a woman suspects that she has been a victim of this sort of assault. More recently, a

similar drug, GHB (gamma-hydroxybutyrate), has appeared on the illicit market. This drug has most of the properties of the benzodiazepines, but has never been used clinically in North America. It is a colourless, tasteless liquid that has also been widely reported as a date-rape drug. As with the benzodiazepines, a combination of GHB with alcohol is particularly risky, and because the drug is a liquid, it is more difficult to provide an accurate dose.

Points to Consider

- Very few patients need to take benzodiazepines for long periods of time. It is important that such patients accept their need for the drugs and do not become intimidated by bad publicity to the point where they discontinue use of the drug. If this occurs, one may have reduced the usage of the drug, but at the expense of patient health.

- The decision to use drugs in this class resides with the physician, and the appropriate use of these agents is patient-specific. The physician is often under pressure to prescribe these drugs, and although they may feel uneasy about writing the prescription, the demands by the patient and the relative safety of the drugs may tip the balance in favour of their use. Clearly the physician has the responsibility of careful prescribing, but the point that these drugs are not the answer to life's problems needs to be made forcefully and repeatedly.

- These drugs share with alcohol the ability to lower inhibitions and impair memory. They are not widely abused on the street, although they are available. Rohypnol®, which belongs to this class, has been identified as a date-rape drug. In this sense, however, any sedative-hypnotic drug can contribute to sexual assault.

- Drugs for anxiety and insomnia can contribute significantly to the quality of life for some individuals, but current medical opinion favours the use of the benzodiazepines in the short-term only, except for a very few patients. It is sensible to try non-pharmacological management for these conditions first. Patients should be cautioned not to ask the doctor for these agents, but to accept his or her diagnosis and management strategy. It is particularly inadvisable to use the agents at higher doses than specified, to continue to use beyond the length of time recommended, or to mix several different agents in this class with alcohol or with each other. Equally, the drugs are not useful in depression and may actually exacerbate the problem.

2.3 Other Sedative-Hypnotic-Anxiolytic Drugs

2.3.1 Overview

A sedative drug calms the patient to the point where sleep may supervene. A hypnotic drug produces sleep directly. The first important agents in this group were the barbiturates. These are derivatives of barbituric acid, and differ from

each other mostly in duration of action and routes of administration. The use of these agents as sedative-hypnotic drugs was once widespread, but over the last few years they have become less and less popular, largely because the benzodiazepines have proved to be safer and almost as effective. Agents such as pentobarbital (Nembutal®) and thiopental (Pentothal®) retain some use in anaesthesia, and phenobarbital is still sometimes used in convulsive disorders, although less frequently. Other combination drugs sometimes include barbiturates; the drugs Fiorinal® and Fiorinal-C® (both requiring a triplicate prescription) contain respectively ASA, caffeine and butalbital, and the same combination with codeine added. The barbiturates have no pain-relieving properties; in fact they may make the person more sensitive to pain. On the other hand, these agents are sometimes used in combination for simultaneous sedation (the barbiturate) and analgesia (the ASA or ASA-codeine combination). Long-term use of these drugs results in tolerance, and abrupt cessation is associated with a dangerous withdrawal syndrome. There have been plenty of cases of psychological dependence that have been initiated because of the use of these drugs as sedatives.

When it was realized that addiction to the barbiturates was not infrequent, there was a concerted effort to develop new drugs that were sedatives without addiction liability. The attempts were not successful, but the products generated were marketed for a number of years and produced some significant problems of their own. The first drugs were glutethimide, the notorious thalidomide, and methyprylon (Noludar®), all of which have now been withdrawn. From the addiction perspective, possibly the most important drug in this class was methaqualone (Quaalude®, Mandrax®) which has long been withdrawn from the market in Canada, but which is still sometimes encountered. Meprobamate (Equanil®, sometimes known by its old brand name Miltown®) is an anti-anxiety agent, which, although it still exists both alone and as the combination 282-Mep®, is very seldom used. As far as can be judged, it does not represent an abuse problem of any significance. A related drug is used as a skeletal muscle relaxant. This is carisoprodol (Soma®), which is metabolized by the body to meprobamate. Cases of abuse of this agent have been reported, but are rare.

More recently, two other drugs have appeared, one for anxiety and the other for sedation. Buspirone (Buspar®) is an agent which has some features in common with the benzodiazepines, but probably exerts its action by a different mechanism. Unlike the benzodiazepines, it has no muscle relaxant properties, but it can produce drowsiness, and it is likely to interact with other agents that affect brain function. Buspirone abuse seems to be very rare. It has therefore been recommended for use by recovering addicts who require a benzodiazepine-like drug; however, Buspirone, may not be as effective as the benzodiazepines. Zopiclone (Imovane®) is a compound that is structurally unrelated to the benzodiazepines, but in most other respects is similar, including the molecular mechanism of action. Few cases of zopiclone abuse have been reported, but the liability for abuse is certainly present, and on the

basis of forensic data after traffic fatalities, one paper suggested that zopiclone should be used with great care. A similar drug, although chemically from a different family is zolpidem (Ambien®), which is currently available in the U.S., but not in Canada.

Points to Consider

- Many of the older sedative drugs have been almost completely superseded by the benzodiazepines. It is worth reflecting that, for each new agent developed to deal with insomnia or anxiety, the abuse liability has been underestimated! If, in the future, new agents such as buspirone or zopiclone succeed the benzodiazepines, there is no reason to believe that we will not make the same mistake. Thus, while problems with drugs like methaqualone will probably continue to decline, we now encounter difficulties with the benzodiazepines, and can anticipate difficulties with some of the recent alternatives. A sedative/anti-anxiety drug with negligible abuse liability may prove to be impossible to design, although there is some evidence that agents such as buspirone may have a lower abuse liability than the benzodiazepines.

2.4 Stimulants

2.4.1 Overview

Stimulant drugs include cocaine, amphetamines and methylphenidate (Ritalin®, Concerta®). Cocaine was previously used as a local anesthetic, but currently there is no legal source of cocaine except in a laboratory setting. The amphetamines used to be widely available and found significant use as appetite suppressants. They are now used only for narcolepsy (uncontrolled episodes of sleep), psychomotor disorders such as epilepsy or Parkinson's disease, and what used to be called "minimal brain dysfunction" in children. This condition is now named "attention deficit/hyperactivity disorder" (ADHD) and is a relatively frequent syndrome in children. Those who suffer from ADHD are disruptive and have a short attention span. These children are usually of normal intelligence, but present a significant problem for their parents and teachers. An adult form of ADHD has been identified. Methylphenidate is used exclusively for ADHD, and its use is very widespread. Concerta® is a sustained-release form of methylphenidate that is being used instead of Ritalin®. Because the brand names are different,it will be easy for people to assume that Concerta® is a completely different drug, but the active ingredient is the same.

It is a largely unexplained paradox that drugs that are stimulants actually help children who are over-active. The drugs do not improve behaviour as such, but they seem to help children with ADHD to tolerate tasks that are repetitive or boring. Methylphenidate is usually preferred to amphetamine although the drugs are very similar. There is some concern about the use of these drugs in

children; they do reduce appetite, and there is some evidence of growth retardation. ADHD is very disturbing, however, and presently there is not a great deal of choice in therapy. Some children do very well on methylphenidate, and it will continue to be used, although the controversy will probably continue as well. Most evidence suggests that the drug is effective as claimed and its use is not attended by serious adverse effects. Even the widespread view that this condition is over-diagnosed may not be correct. Indeed, it has been suggested that some cocaine addicts abuse cocaine because they have unrecognized ADHD, and are attempting to self-medicate. On the other hand, administration of a drug to children for the benefit of parents and teachers rather than the children is unacceptable to some individuals. It is also important to note that several reports suggest there is significant diversion of prescribed methylphenidate to the illicit market from patients, particularly students, who are receiving this drug for ADHD.[12,13]

Diethylproprion (Tenuate®) is a controlled drug, which is a weak amphetamine-like compound used to decrease appetite as a means of weight control. It has a modest abuse liability, and is not very effective in long-term management of obesity. Mazindol (Sanorex®) and phentermine (Fastin®) are similar drugs. Fenfluramine (Ponderal®, Pondimin®) was a constituent of the notorious "Fen-phen" mixture (fenfluramine and phentermine), and tends to produce sedation rather than stimulation. Although it is claimed to have little or no abuse liability, it is no longer available in Canada.

Amphetamine ("speed") addiction was a very serious problem in the late 1960s. During this period, it became apparent that use of amphetamines, particularly by the intravenous route, significantly reduced both quality of life and life expectancy. In consequence, use declined, although it has recently surfaced again in the form of methamphetamine or "crystal meth," which is a form of amphetamine that can be smoked. Amphetamines are dangerous not only because they have serious and immediate effects on the heart and blood vessels, but also because they tend to make the user violent and paranoid. The drugs produce severe psychological dependence and tolerance to the point where lethal doses can be tolerated by the addict. Locally, there has been an increase in the illicit production and use of methamphetamine in Alberta, particularly in the central and northwest areas of the province. One of the key starting materials for the illicit synthesis of methamphetamine is ψ-ephedrine (pseudo-ephedrine), which is marketed as a decongestant. While ephedrine itself has some stimulant activities, which have led the drug to be illegal in athletic competitions, the toxicity of ψ-ephedrine is low enough for the drug to be available without prescription. Attempts are now being made to control the

[12] Poulin, C. (2001). Medical and non-medical stimulant use among adolescents: from sanctioned to unsanctioned use. *Canadian Medical Association Journal, 165* (8), 1039-1044.

[13] Musser, C.J., Ahmann, P.A., Theye, F.W., Mundt, P., Broste, S.K. & Mueller-Rizner, N. (1998). Stimulant use and the potential for abuse in Wisconsin as reported by school administrators and longitudinally followed by children. *Journal of Developmental Behaviour in Pediatrics, 19*, 187-192.

supply of this compound with a view to making the synthesis of methamphetamine more difficult.

A curious phenomenon, which was quite significant in Alberta and Saskatchewan, is the combined use of pentazocine (Talwin®) and methylphenidate (Ritalin®), known as "Ts and Rs." This drug combination is sometimes called "poor-man's heroin" and there has been very little research carried out on the use and abuse of Ts and Rs. The source of both drugs is diversion from the pharmacy by theft or forged prescription rather than manufacture in illicit laboratories. The possibility of significant health problems from this drug combination is very real, but so little is known about the effects of the two drugs in combination that it is difficult to make any definitive statements. In the U.S., a combination of Talwin® and the anti-histamine tripelennamine ("Ts and blues") is sometimes encountered. Recent reformulation of the oral preparation of pentazocine has made it difficult to dissolve the tablets and then inject them. This has greatly reduced, but has not eliminated, the use of this drug combination. Both counsellors and hospital emergency room personnel claim that the use of this drug combination is decreasing. Recent AADAC data show that two percent of treatment clients reported using Ts and Rs in the previous year, and it was a drug of concern for one percent of clients in AADAC treatment.[14]

Points to Consider

- Clinical use of stimulants is minimal compared with that of the opioids and the benzodiazepines. Use of the amphetamines and methylphenidate is controlled, and survey data suggest that self-reported use of clinically prescribed stimulants is low. However, the abuse of illicit stimulants such as methamphetamine is increasing.

2.5 Performance-Enhancing Drugs

2.5.1 Overview

The misuse of performance-enhancing drugs is a form of drug addiction, which was highlighted by the scandal involving Ben Johnson, a scenario that has since been repeated at almost every world sporting event. Unfortunately, rather than provide an object lesson, these reports may have illustrated the performance gains that can be achieved with drugs. The considerable salaries and prestige that accompany athletic excellence provide a further impetus to attempt any route to improved performance. In addition, our present society is preoccupied with physical appearance, and a route that provides enhanced good looks may prove irresistible. In an effort to discourage the use of performance-enhancing medication, it has been fashionable for the medical profession to question

[14] Ibid, note 2.

whether the drugs produce any significant increase in performance. Even if available evidence from animal studies or human trials is equivocal, the athletes themselves may have clear, if anecdotal, evidence of success. This confusion arises sometimes from the placebo effect, sometimes from the fact that drugs are being used in much higher doses by the athletes than were used in the clinical trials, and sometimes from errors in design or interpretation of the trials themselves. Regardless, in working with addicted athletes, it is important to keep in mind that the perception of the athletes must be taken seriously. Long before medicine accepted the dramatic effects of the anabolic steroids, their properties were well known to athletes in training. The drugs used to enhance performance are listed in Table 5. The stimulants are taken to diminish fatigue, and the opioids to relieve pain, which would otherwise interfere with competition, and to provide a calming effect. These drugs are discussed in Sections 2.4 and 2.1 respectively.

TABLE 5: Drugs Used to Enhance Athletic Performance

Stimulants (e.g., amphetamines)
Opiates (e.g., morphine)
Anabolic steroids (e.g., stanozolol—Stromba®)
Peptides (e.g., growth hormone)
ß-receptor antagonists (e.g., propranolol—Inderal®)
Anti-inflammatory drugs such as corticosteroids
Diuretics (e.g., furosemide—Lasix®)
Nutritional aids/natural remedies etc.

2.5.2 Anabolic Steroids

The anabolic steroids are distinct from drugs like the corticosteroids, such as prednisone, or the female steroid hormones such as estrogen. They are similar to testosterone, and are used clinically in patients who cannot make their own testosterone. Taken in very high doses, these drugs increase muscle mass, although the effects are minimal unless the administration of the drugs coincides with a program of vigorous exercise and appropriate diet. They are used by body-builders and by competitors in other sports where weight and strength are an advantage. They also produce significant psychological changes, including violent behaviour ("roid rage"), which may be characterised as useful in some sports. Most available scientific evidence probably underestimates the weight gain. There is little scientific rationale in the dosage regimens employed to enhance performance; these often involve the use of a combination of different intravenous (or subcutaneous) and oral steroids and trainers usually develop their own "secret formula." These drugs are readily detected and use must be tapered before the event itself if the user is to escape detection during drug tests. There are frequent attempts to devise an anabolic steroid that can escape detection; the latest is tetrahydrogestrinone (THG), for which testing has only just become available, and which threatens to damage the reputation of some athletes whose urine samples have been stored and can be re-tested.

The adverse effects of these drugs have been given a lot of prominence in an effort to discourage their use. The drugs produce a suppression of the natural male hormone, testosterone, which is also present in women, although in smaller amounts. In users of anabolic steroids, the hormone is provided from outside, and thus the body automatically shuts off its own production of testosterone. Because the testicles are no longer required to produce the hormone, shrinkage of the testicles occurs in more than half the male athletes who use the drugs. On the other hand, the large amounts of the hormone that are administered exceed the body's normal production, and thus the drugs may increase libido in both men and women. Failure of erection and ejaculation in males sometimes occurs, particularly when administration of the steroid is stopped or diminished abruptly. The drugs produce masculinization in women, which may be only partially reversible if the drug is discontinued. Acne and disorders of blood lipids may occur in both sexes. These agents can cause liver damage, and some cases of steroid-dependent liver tumours have been reported. These tumours require the presence of anabolic steroids to grow, and can prove rapidly fatal. The extent of liver problems depends on the dose and how long the drugs have been used, as well as other unknown factors. The effects may be mild and reversible although a few well-publicized deaths have occurred. In children, anabolic steroids can cause permanent stunting of growth by interfering with the normal process of joint development. The psychological problems with the drugs can be very severe. Unfortunately, most users believe that many world-class athletes have used these drugs with no ill effects.

2.5.3 ß-Receptor Blockers

These drugs have a calming effect and are useful under circumstances where the stress associated with competition would provide a distraction by raising heart rate. The drugs are used in sports like archery or shooting, but are a considerable disadvantage in sports that require vigorous physical performance. These drugs are widely used for a variety of clinical conditions, and side effects were generally regarded as minor, although these drugs can accelerate artery disease, and sexual function in males can be impaired.

2.5.4 Diuretics

Diuretics are used to produce a dramatic loss in weight so that a wrestler or boxer can qualify for a division below their actual weight category. They have no other advantages. These drugs are used clinically to assist in draining fluid, where the most popular agent is probably furosemide (Lasix®), which produces a dramatic and rapid loss of water and weight. The problems with this drug are dehydration, alterations in blood lipids and reduced sexual performance in males. Changes in the composition of the blood can cause problems, particularly in someone who is doing vigorous exercise.

2.5.5 Peptides

Some athletes inject growth hormone. The agent has some anabolic effects, but its effects on growth of normal individuals are still controversial. Another "forbidden" compound in this class is erythropoietin, which stimulates production of red blood cells and thus produces a sort of drug-induced "blood doping." The side effects and benefits of these agents are not well established.

2.5.6 Other

Athletes often take a variety of unproven agents in order to enhance performance. These may be the "health food" type of supplements, or herbs or animal material whose biological action has never been convincingly documented. Because there are frequent injuries to elite athletes, these individuals may also be receiving appropriate medication to reduce inflammation or speed healing. In addition to the drugs discussed here, some sports also include drugs that are illicit, but not performance enhancing in their list of banned substances. A disturbing illustration was the case of the Canadian snowboarder, Ross Rebagliati, who had trace amounts of cannabis derivatives in his urine, which nearly deprived him of a gold medal. The issue here is more ethical than pharmacological.

Points to Consider

- Discussions of drug abuse do not usually cover the use of performance-enhancing drugs by athletes, but it may be time to include this area. Certainly the drugs are popular in schools, fitness facilities and health clubs.
- The Canadian Centre for Ethics in Sport has produced a number of resources including the *Drug Classification Manual*. These resources are available for a nominal charge via the website of the Sports Medicine Council of Alberta.[15]
- It is important that young athletes are told more than "do not use illegal drugs;" helpful advice on nutrition, lifestyle and coaching may help the "clean" athlete to be competitive when faced with other contestants who may be using performance-enhancing drugs.

[15] Sports Medicine Council of Alberta (online at: www.sportsmedicinecouncilofalberta.ca).

2.6 Miscellaneous Agents

2.6.1 Ketamine

Ketamine is a "dissociative anesthetic" that is still sometimes used in clinical medicine. It is pharmacologically related to phencyclidine, and produces a curious sensation that the experience is happening to someone else, something which is useful when surgery in a fully conscious patient is necessary. About eight years ago the drug started to become popular as part of the "rave" scene, where it became known as "K" or "Special K." The drug works by blocking a subtype of receptors ("NMDA receptors") for a widespread brain neurotransmitter called glutamate. The exact mechanism by which this action produces the sensation of depersonalization is not known.

Recreational use of ketamine produces a sensation of wisdom and power, as well as permitting the user to experience new thoughts and perceptions that may be helpful and pleasurable, but can also be frightening. Individuals who have used ketamine sometimes want to repeat the experience, although it does not seem to be addicting in quite the same way as, for example, cocaine. There are isolated reports that it can cause permanent changes in thought and mood, particularly in young people where neuronal development is taking place. There have also been a couple of cases of death attributed to ketamine. Overall, we do not know a great deal about the recreational use of this drug, but the uncertainty as to source and dose as well as the adverse effects, makes its use highly unwise.

2.6.2 Amyl Nitrate

Another unusual drug of abuse is amyl nitrate. This drug is used for the management of angina; a painful disease of the heart arising from partially blocked coronary arteries. Both amyl nitrate and some analogues (not controlled by law) are occasionally used as drugs of abuse. Inhalation of the agent produces a sudden drop in blood pressure that results in a "floating" sensation. The drugs appear to be particularly popular in the male homosexual community, possibly because in addition to relaxing blood vessels, they also relax other involuntary muscle, thus making anal intercourse rather easier. There is little available literature on these agents as drugs of abuse. Newspapers have reported that drugs such as butyryl nitrate (referred to as "locker room" because of the smell, or more simply as "poppers") are widely available in nightclubs, particularly gay nightclubs, but there is little reliable information about the prevalence of these agents. Use of this drug was also reported by respondents participating in a study of the "rave" scene in Alberta.[16]

[16] Fluet-Howrish, C., Hutton, S., & Harvey-Jansen, Z. (n.d.). *Raving in Alberta: Understanding the youth perspective* (draft report). Edmonton, AB: Alberta Alcohol and Drug Abuse Commission.

2.6.3 Sildenafil

Media reports and research from elsewhere suggest that sildenafil (Viagra®) is being combined with MDMA (ecstasy) to give a combination known as "sextasy." MDMA produces feelings of closeness and sexual arousal, but also tends to produce impotence, particularly after prolonged use. The combination of MDMA and sildenafil is often effective for the purpose intended, but can also be associated with problems. First, the risk of unprotected or otherwise risky sex is increased. The drug is reported to be particularly popular with male homosexuals, a group that is already at some increased risk of HIV infection. Second, the combination can result in erections that do not subside for long periods, sometimes hours, and this condition can be alarming and painful, sometimes resulting in damage to the penis. Finally, although the drugs work by different mechanisms, they both have effects on the cardiovascular system. A number of newspaper articles have suggested that the combination can produce cardiac dysrhythmia, although there have been no published case reports in the medical literature.

Points to Consider

- As new drugs are discovered, some will prove to have effects on the brain, which a proportion of the public will find enjoyable. In a well-meaning attempt to prevent problems, this is often given wide publicity, with the result that those who would never have thought of taking the drug will attempt to procure it. This is exactly the reverse of what is intended! Considerable discretion must be used when publicizing information about drugs that have some abuse liability, but whose properties remain largely undiscovered by the general public.

2.7 Marijuana

There has recently been a resurgence of interest in the medical use of marijuana and similar materials. It has been known for many years that marijuana can have an anti-nausea effect, and this led to the development of the drug nabilone (Cesamet®), which belongs to the cannabinoid class, the same group of drugs that provide the active ingredient in marijuana. Nabilone is licensed for use **only** for the management of nausea following cancer chemotherapy where it is very effective, and it does not seem to have attracted much attention from the drug-using section of society. Perhaps this arises because although up to about 40% of patients will experience some measure of perceptual change with nabilone, the effects are less dramatic than with marijuana, and the availability of nabilone is much less than that of marijuana or hashish. More recently, the active ingredient of marijuana itself, Δ^9-tetrahydrocannabinol sometimes called dronabinol (Δ^9-THC, Marinol®), has become available for the same purpose, although the development of ondansetron (Zofran®), which is a highly effective anti-nauseant that lacks the mood-altering effects of the cannabinoids, has made these agents a lot less popular. The advantage of the smoked form of cannabis

over the tablet forms of nabilone or dronabinol is that it can easily be titrated to a point where the user feels that the nausea is under control without intrusive adverse effects. The delay in response after oral administration precludes this possibility, and this may have contributed to the problems with these oral forms. Current research is directed towards an aerosol preparation of Δ^9-THC that would provide a similar rapid response without the necessity for inhaling quantities of tar. This product is, unfortunately, a few years away from being commercially available.

Although the use of cannabinoids for nausea associated with cancer chemotherapy is established, a variety of other uses have been suggested over the years. The drug has some effects on the canal that drains the eye, and is thus useful in increasing the drainage in patients with glaucoma, a condition of elevated intra-ocular pressure that can cause blindness. This effect of marijuana is not in dispute, although there are other drugs that have a similar effect. The problem is that the effects are transient, and thus, either the pressure would again increase or the individual would require additional marijuana. One estimate suggests that, to provide adequate control of intra-ocular pressure with marijuana, an individual would have to smoke about 4,000 joints a year. Although this observation has been disputed, certainly cannabis has a rather short duration of action in terms of its effects on mood, and it would not be surprising to find that the effects on intra-ocular pressure were similarly short-lived. This suggests, however, that synthetic derivatives, perhaps with a reduced tendency to metabolism or storage in fat, might prove useful, and it clear that the American Academy of Ophthalmology is supportive of further study. It has been demonstrated that activation of the cannabinoid receptor does lower intra-ocular pressure, but another small study suggested that tolerance developed to the effects and all the patients in the study chose to discontinue therapy with cannabis. There have been no further advances in this area.

A use of marijuana for which there is a massive amount of anecdotal information, but fewer clinical studies, is in appetite promotion. Users of marijuana have reported for years that it increases appetite, and there are a number of conditions in which this property would be desirable. Terminal conditions including advanced cancer and AIDS are often accompanied by *cachexia*, or "wasting," in which all interest in food vanishes. An agent that stimulates appetite would be welcome in this group of patients. There is a significant amount of evidence that body weight is maintained and appetite increased in patients with cachexia who are treated with cannabis, and one article describes this effect as "proven."[17] Despite this, there have been no large scale randomized controlled trials and the issue has not been completely resolved. It seems probable, however, that by the next edition of this report, this will be another established use for the drug.

[17] Walsh, D., Nelson, K.A., & Mahmoud, F.A. (2003). Established and potential therapeutic applications of cannabinoids in oncology. *Support Care Cancer, 11* (3), 137-143.

For many years it was claimed that there was no evidence that marijuana relieved pain, but more careful studies have shown that the drug may have pain-relieving effects. This is based on animal studies, in which the cannabis receptor appears to have some link to the opioid receptors in the central nervous system, specifically in the pain pathways in the dorsal horn of the spinal cord. Analgesia was also demonstrated in a rather unsatisfactory human study, but two more recent and better-conducted trials showed no significant effect. It is not, at present, clear whether the drug is sufficiently potent for its use to be rational, nor is its adjuvant effects known in patients already receiving pain-relieving drugs.[18]

Other uses are even more speculative. We have few drugs which materially affect the development of multiple sclerosis, but there have been a number of claims from those who suffer from this devastating disease that smoking marijuana helps. Other individuals have claimed that the drug helps spasticity, while it has also been claimed that the drug is useful in controlling seizures. For this last claim, at any rate, there is some supportive animal data.[19] A recent paper suggested that the drug might also be useful in treating amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) but provided no supporting evidence.[20] Use of cannabis in animal models of the condition provides promising results, but a very recent article points out that there have been no more than 10 studies in humans, involving a total of fewer than a hundred patients. While the data are equivocal, the better studies tend to show less promising results.[21] Under the present legislation in Canada, where individuals may be permitted to possess marijuana for medical reasons, a significant number of such patients are sufferers from multiple sclerosis. The passionate support that some of these individuals provide for continued availability of cannabis to manage their illness, is difficult to ignore, but clearly much more work is needed.

Cannabis has also been recommended for a few other conditions, including anxiety and migraine headaches, but there is essentially no evidence of effectiveness. The problems of the medical use of marijuana are four-fold. First, the effects of the drug are relatively ephemeral. It is eliminated from the body rather slowly, but the active ingredient is rapidly cleared from the blood, both by metabolism and by redistribution into fat. For marijuana to be useful for any chronic condition, it would have to be used at such frequent intervals that it might be impracticable. Clearly for short-term use, such as for the nausea that

[18] Rice, A.S. (2001). Cannabinoids and pain. *Current Opinion in Investigational Drugs, 2*, 399-414.

[19] Wada, J.A., Wake, A., Sato, M. & Corcoran, M.E. (1975). Antiepileptic and prophylactic effects of tetrahydrocannabinols in amygdaloid kindled cats. *Epilepsia, 16*, 503-510.

[20] Carter, G.T. & Rosen, G.T. (2001). Marijuana in the management of amyotrophic lateral sclerosis. *American Journal of Hospice & Palliative Care, 18*, 264-270.

[21] Killestein, J., Uitdehaag, B.M. & Polman, C.H. (2004). Cannabinoids in multiple sclerosis: Do they have a therapeutic role? *Drugs, 64*, 1-11.

accompanies cancer chemotherapy, or as a pain-relieving drug or an agent for cachexia, this limitation would be much less serious. In addition, the possibility exists of circumventing this problem by developing analogues of the active ingredient of marijuana, Δ^9-THC, which are less fat-soluble and/or less susceptible to metabolism. Even those authorities that have taken a supportive view of medical marijuana tend to favour the oral administration of Δ^9-THC derivatives, which delays the onset but prolongs the effects, rather than smoking the plant itself. Smoking, of course, not only reduces the duration of action, but also carries risks associated with the inhalation of tar. Again, this becomes a debatable issue; use for short-term control of pain or nausea may not be attended by any significant problem, but for chronic therapy, inhalation of smoke poses a considerable risk.

The second limitation is that the drug produces behavioural and perceptual changes that for most people are not compatible with chronic use. While a significant portion of the population enjoys a controlled and transient experience with marijuana, a much smaller percentage would welcome being stoned the whole time. So far, we have had little success in devising a derivative that is devoid of effects on the brain, although nabilone is reputed to be less active than dronabinol. On the other hand, we know now that there are at least two different sorts of cannabis receptors, one of which is located primarily in the brain, and the other in the intestine. It is very likely that the use of synthetic cannabis derivatives may enable us to separate out the desired from the unwanted effects, but the development and testing of these compounds is still some years away.

Thirdly, the perceptual distortions that the drug produces make it essentially impossible to use double-blind methodology in clinical trials. In double-blind experiments, neither the subjects nor the person assessing improvement knows whether the individual belongs to the experimental or control group. This methodology tends to underestimate the effectiveness of the drug in real clinical use, but is an important part of drug trials.

Finally, the political issues surrounding the production and testing of the cannabis plant for management of disease have dramatically diminished progress in the area. The story of Canada's ill-fated attempts to produce a standardized cannabis crop need not be related here. The policy that failed to support any kind of testing program for thirty years and then approved a drug whose beneficial effects have not been established, to any self-selected individuals who can persuade a suitably licensed health professional to support their application, is difficult to defend. It is equally difficult to tell someone who believes, perhaps correctly, that the drug has helped them, that they cannot legally use it. Further, there was, for a long time, no legal source, and a person who did supply the drug to an approved user could be charged with trafficking. The entire process clearly needs to be reviewed in the light of objective evidence, clinical experience and patient choice. The one fact that has made the

situation less dangerous is that in most patients the drug is at least reasonably safe.

Currently we see marijuana and similar drugs like hashish as being agents that are of interest primarily because they can be involved in drug abuse. Further information from clinical trials that are being planned or are in progress may produce a picture more like that seen with the opioids, in which the abuse liability still exists, but where there are marked clinical benefits as well. In the case of marijuana there is one additional complication; the cannabis plant itself has considerable value to society as a source of fibre, and strains exist which are low in Δ^9-THC but useful for fibre. These strains are not readily distinguishable on sight from those that are high in Δ^9-THC, and this has led many jurisdictions to forbid cultivation of all cannabis plants. The marijuana plant has effects that are of considerable interest, and the products derived from it are commercially and clinically useful. How we balance the abuse liability of this drug, its potential for clinical use and its agricultural value will be interesting to see.

3. Non-Prescription Drugs With Abuse Liability

3.1 Overview

Non-prescription medication is generally less toxic and also less effective than prescription medication, but this does not mean that it is devoid of abuse liability. In fact, most classes of drugs used for non-medical purposes have some members that are available without prescription; the opioids are represented by codeine, there are over-the-counter sedative-hypnotic drugs, and for many years, anyone could buy a nasal inhaler which contained an amphetamine. The present "wake-up" preparations available from pharmacies mostly contain caffeine. The major problem here is probably codeine, which has already been discussed, but there are other classes of drugs about which some care is necessary.

3.2 Antihistamines

The antihistamines are a class of drug used for symptomatic control of hay fever and related allergic conditions. The newer antihistamines such as terfenadine (Seldane®) and astemizole (Hismanil®) lack effects on the brain and are thus largely devoid of abuse liability. In fact, until recently, terfenadine and astemizole were regarded as very safe, although it is now known that they interact in a potentially fatal fashion with the macrolide antibiotics such as erythromycin (Erythrocin®) and many of the antifungal drugs related to ketoconazole (Nizoral®), including fluconazole (Diflucan®), itraconazole (Sporanox®) and miconazole (Micatin®). The traditional antihistamines have pronounced sedative activity, and they are often the major constituents of non-prescription sedative drugs. Agents like dimenhydrinate (Gravol®) are antihistamines that are used in the control of motion sickness, and also have sedative effects. These agents pose some hazard in accidental or suicidal overdose. Incidence of true addiction has usually been regarded as low, on the grounds that addicts prefer agents that produce a more pleasant sensation. However, there have been reports that some of these drugs are being used on the street; dimenhydrinate seems to be the most popular, but certainly tripelennamine (Pyribenzamine®) and cyclizine (Marezine®) are abused in the United States. The effects are confusion, sedation and sometimes hallucinations.

3.3 Diet Aids

Most non-prescription diet aids are food-substitutes, but there are a significant number of unproven herbal remedies on the market, and some benzocaine-containing preparations, often marketed for sore throat, that have some effects

on appetite. There are two problems with these agents. The first is that the preoccupation with weight, which is so characteristic of our present society, will lead to compulsive use of almost anything that holds even a remote promise of success. There have been cases of people who have made themselves seriously ill (one died) from the use of syrup of ipecac. This non-prescription product is an emetic, which is used to make children vomit if they have taken some potentially dangerous compound by mouth, but bulimic patients may use it after they have eaten and as a result can become very sick. The second problem is that evidence for the success of ANY chemical approach to weight loss is, at best, tenuous. In some instances, there will be some loss of appetite and some initial weight loss, but tolerance rapidly develops. Unfortunately the simple formula of eating less and exercising more still seems to be the only means of long-term weight control. Fad diets and weight control products usually produce a temporary loss in weight, which is often followed by an increase that exceeds the loss during the diet. Prescription products for weight loss are detailed in Section 2.4, Stimulants.

3.4 Laxatives

An unlikely group of agents with abuse liability are the laxatives. This was a particular problem in the early years of the 20th century, in which bowel movements were equated with inner cleanliness. Tolerance to the drugs develops to the point where normal bowel movement will become difficult in the absence of the laxative. Prolonged use can cause a variety of problems with the lower bowel. These drugs have no direct effects on the brain, but their actions are sufficiently impressive for dependence to arise even today, particularly among the elderly.

3.5 Herbal Preparations

A full discussion of herbal preparations is beyond the scope of this report. While a significant number of modern drugs have been developed from herbal preparations, and there is an increasing interest in the use of ancient herbal pharmacopoeias as a starting point for the development of new therapeutic approaches, our information about the constituents and action of most of these remedies is rudimentary. In an addictions context, herbal preparations may have some addiction liability, may have the ability to help deal with cravings, and may alter the action of other drugs.

If we ignore agents such as opium or cannabis products that have already been discussed, the number of preparations with clear addiction liability is limited. There have been anecdotal reports of abuse of St. John's Wort, an agent that is recommended for the treatment of depression and anxiety, although the compound

has also been recommended for reduction of craving in alcoholics.[22] Kava-kava has also been recommended as an antidepressant drug, but has been associated with potentially fatal hepatoxicity and, in consequence, has been banned in Canada. Agents like psilocybin that are found in "magic mushrooms" are not generally regarded as herbal medicines nor are they legally available, although peyote is used as a sacrament in the Native American Church of the Navajo peoples, with permission from the U.S. Government.

There has been a recent increase in the interest of the use of centrally acting plants in reducing cravings. Early experiments by Hoffer[23] that suggested the approach might be effective proved to be very controversial, but more recently the hallucinogenic alkaloid ibogaine from the iboga bush has been recommended as an anti-craving agent, based mostly on animal experiments.[24] It remains to be seen whether this proves to be widely effective in humans.

A final point is that St. John's Wort seems to increase the speed at which methadone is metabolized, so that the duration of action is reduced. In a recently reported study, those on methadone maintenance who took St. John's Wort showed signs of withdrawal.[25]

Points to Consider

- The point raised earlier about publicity for new, potentially addicting drugs applies with particular force to non-prescription medication, because control of the distribution of this class of agent is even more difficult than with prescription drugs. The news media can be an important ally in this regard, and those connected with the addictions would be well advised to forge mutually beneficial links with local papers and radio and TV stations. The media share the concern of the public about substance abuse, and usually strive to report the issues accurately. However, they need not only good factual information, but also sometimes advice on the reporting approach or even whether the story should be used at all. Those involved in preventing or treating addiction should be available and enthusiastic about helping the media in this regard.

- The huge issue of lifestyle, diet and body image has been implicit in a lot of the work on modification of drug-seeking behaviours, but has seldom been tackled as a separate topic. Where the phenomenon involves the use of pharmacological attempts to reduce weight, those connected with the addictions should be prepared to get involved.

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[22] De Vry, J., Maurel, S., Schreiber, R., de Beun, R. & Jentzsch, K.R. (1999). Comparison of hypericum extracts with imipramine and fluoxetine in animal models of depression and alcoholism. *European Neuropsychopharmacology, 9*, 461-468.

[23] Hoffer, A. (1965). D-Lysergic acid diethylamide (LSD): A review of its present status. *Clinical Pharmacology and Therapeutics, 39*, 183-255.

[24] Maisonneuve, I.M. & Glick, S.D. (2003). Anti-addictive actions of an iboga alkaloid congener: A novel mechanism for a novel treatment. *Pharmacology, Biochemistry and Behavior, 75*, 607-618.

[25] Eich-Hochli, D., Oppliger, R., Golay, K.P., Baumann, P. & Eap, C.B. (2003). Methadone maintenance treatment and St John's Wort: a case report. *Pharmacopsychiatry, 36*, 35-37.

4. Drugs Which Are Over-Used But Not Addicting

There are a variety of medications which are over-used, or where the benefits are minimal, but for which true addiction is rare. Agents such as acetaminophen (Tylenol®) are very widely used but the drug has no effect on the brain, nor any obvious effect on the healthy body, and so people use the drug routinely but seldom compulsively, unless it is supplemented by another drug such as codeine.

The reasons for over-use of non-prescription medication are complex but include some fundamental features of human nature. Sir William Osler (1849-1919), the Canadian-born physician often regarded as the father of modern medicine, considered that the desire to take drugs was an important distinction between animals and man. This clearly stems from the entirely rational desire to avoid or rapidly resolve any sort of discomfort. The development of large numbers of effective but potentially dangerous medications has left most individuals with the concept that any condition can be treated with drugs, and if the condition is trivial, non-prescription medication may be the answer. This view is perpetuated by skilled advertising to the general public. It is probably true that the majority of medication that is available without prescription is used inappropriately and excessively. Yet another problem is the potential interaction between needed prescription drugs and self-medication with non-prescription products. ASA, decongestants, antihistamines, antacids and, indeed, almost any medication other than that applied locally to the skin, all have the possibility of significant interactions with prescription drugs.

Points to Consider

- This matter reduces to the issue of patient education and sometimes to the issue of continuing medical education. Those connected with the addictions need effective liaison with other healthcare professionals to try to reduce the consumption of unnecessary drugs. Not only is this potentially damaging to patient health—after all, addiction is only one of a number of hazards of over-use of therapeutic agents—but is also a substantial and unnecessary drain on dwindling healthcare resources.

- The Alberta Pharmaceutical Association has had continuing education programs on the subject of non-prescription medication and is committed to the concept of appropriate drug use.

5. Use of Medical Drugs in Addicted Patients

5.1 Overview

In this report so far, we have discussed medical drugs that addicts like to use. In this section we will discuss drugs that the medical profession may wish to use in treating the addict. Addiction is often accompanied by a variety of psychiatric syndromes and the attending physician may elect to use drugs to treat the mental illness. There is often widespread confusion among addicts, treatment agencies and the general public about this entire area. Someone who is a depressive who is being managed successfully with antidepressants is not addicted to the antidepressant, any more than a diabetic is "addicted" to insulin. Nonetheless, well-meaning individuals will sometimes attempt to persuade patients who are addicted to other drugs that the medication they are taking is merely another form of their addictive problems, and this may lead the person to abandon medication which is critical for their mental well being. This is a problem in which there is no substitute for real education, because managing depression or psychosis with drugs has almost nothing to do with addiction.

5.2 Depression

This condition is a lot more serious than attacks of temporary sadness, which afflict everyone. The depressive has low self-esteem, finds enjoyment difficult, and will often attempt suicide, or at least consider it. The condition is chronic, and exhortations to "count one's blessings" or "cheer up" are totally ineffectual. The condition may not respond well to counselling alone, but a program of psychotherapy is often a critical component of the overall management of the patient. Depression is frequently associated with dependence on alcohol or other drugs.

The condition is managed by three major classes of drugs. These are the tricyclic antidepressants such as amitryptaline (Elavil®), the monoaminoxidase inhibitors such as phenelzine (Nardil®) and the 5-HT uptake inhibitors such as fluoxetine (Prozac®). There are also a few additional antidepressant drugs that do not fit into the three main categories. All these drugs share an ability to enhance the activity of pathways in the brain, which use noradrenaline and/or serotonin as neurotransmitters. A list of currently available antidepressants is provided in Table 6.

The original antidepressants were the tricyclic drugs, and there are a substantial number of these still available and widely used. There are a number of problems with these agents, mostly related to adverse effects, and this led to the development of the second class, the monoaminoxidase inhibitors (MAOIs). Most of the MAOIs require strict diet control, because there are life-threatening interactions possible with a variety of drugs and chemicals in common

foodstuffs, and this limits their usefulness. The more selective MAOI, moclobemide, does not require the dietary restrictions, but some physicians believe that it is also less effective.

TABLE 6: Antidepressant Drugs

Tricyclic & similar antidepressants

- Amitriptyline (Elavil®)
- Clomipramine (Anafranil®)
- Desipramine (Pertofrane®)
- Doxepin (Sinequan®)
- Imipramine (Tofranil®)
- Maprotiline (Ludiomil®) (tetracyclic)
- Nortriptyline (Aventyl®)
- Trimipramine (Surmontil®)
- Monoaminoxidase inhibitors

Phenelzine (Nardil®

- Tranylcypromine (Parnate®)
- Moclobemide (Manerix®) (Type A selective)

Specific serotonin reuptake inhibitors

- Citalopram (Celexa®)
- Fluoxetine (Prozac®)
- Fluvoxamine (Luvox®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)

Noradrenaline/serotonin reuptake inhibitor

- Venlafaxine (Effexor®)

Other

- Trazodone (Desyryl®)
- Tryptophan (Tryptan®)
- Bupropion (Wellbutrin®, Zyban®)

The advent of the specific serotonin reuptake inhibitors (SSRIs), the best known of which is Prozac®, has revolutionized antidepressant therapy. The SSRIs are not noticeably more effective at alleviating depression than the tricyclic antidepressants, but they have fewer side effects, at least initially, and seem to be better able to restore a fully normal affect. These drugs have been very successful in the management of those who are clinically depressed, but their very success has created some problems, also. There has been a regrettable tendency to use the drugs for situations in which the patient is not depressed but grieving, which may be a natural and healthy occurrence and one that does not require drug therapy. The adverse effects of this group of drugs were initially regarded as relatively minor; impotence in men and difficulty in reaching orgasm in both sexes. Early reports suggested that patients treated with fluoxetine showed a higher incidence of suicide, but this phenomenon is not unique to fluoxetine. In those who are severely depressed, the condition may so incapacitate a patient that suicide, although seen as desirable, requires more energy than can be mustered. A small improvement in the depression may thus

increase the likelihood of suicide. Patients who are suicidally depressed need very careful monitoring, even if their depression is improving. More recently there have been some disturbing reports of long-term effects such as movement disorders and memory loss after chronic use of the SSRIs.

Recently there have been a number of reports that suggest that these drugs are generally ineffective in teenagers, and the issue of suicide while taking the drugs has also been raised again. This remains controversial, but the majority view is shifting towards these drugs being used rarely or never in people under 20 years of age.[26] Finally, there is a significant withdrawal syndrome when these drugs are stopped abruptly. While this is not life threatening, it is disturbing and inconvenient. Paroxetine seems particularly liable to produce this effect.

More recently, another agent with a mode of action similar to the tricyclic antidepressants but with a much more selective activity profile has been developed. This is venlafaxine (Effexor®), which works at both noradrenalin and serotonin-containing nerves, but has little action at other sites. Because it is selective but has a slightly different range of action than the SSRIs, it was hoped that it would be useful in patients who respond poorly to this latter class of drugs. In fact, it seems very much like the other SSRIs, but it does have a marginally more rapid onset. Trazodone is chemically and pharmacologically different from the other antidepressants and, while effective, is not currently a first-line drug. L-tryptophan is an agent whose use is based on theoretical grounds; evidence of its effectiveness, either alone or in combination with other antidepressants, is presently equivocal.

Bupropion was never regarded as a highly effective antidepressant, although there is good evidence that it can be very useful in some patients. Patients, who do not wish to use the SSRIs because of impairment of sexual function, can sometimes be managed successfully with bupropion. As Zyban®, however, it has suddenly gained prominence as an adjunctive therapy for smoking cessation, where its effects have been well established. Little is known about the mechanism of the effects, but since this property is not shared to the same extent by other and more potent antidepressants, the effects may be unrelated to antidepressant activity.[27]

These agents do not elevate the mood of normal patients who are not depressed, and are usually slow acting. This means that the depressed patient will not start to get the benefits of the drug for two or three weeks after therapy has started, and this needs to be explained to the patient. With the single exception of the MAOI tranylcypromine (Parnate®), which has a weak amphetamine-like effect and some mild abuse liability, none of these drugs should give rise to any

[26] Whittington, C.J., Kendall, T., Fonagy, P., Cottrell, D., Cotgrove, A. & Boddington, E. (2004). Selective serotonin reuptake inhibitors in childhood depression: Systematic review of the published versus unpublished data. *Lancet, 363*, 1341-5.

[27] Rose, J.E. (1996). Nicotine addiction and treatment. *Annual Review of Medicine, 47*, 493-507.

concern about addiction. This does not mean that the drugs are universally safe, but there should be few concerns about the use of antidepressant drugs in an addict who is undergoing good medical treatment for depression. Whether the depression that often appears in early recovery should routinely be managed with antidepressants remains controversial, but in the absence of a clear diagnosis of depression that is distinct from the emotional turmoil that accompanies abstention, these agents should probably be avoided.

5.3 Bipolar Disorder

This is a very disturbing condition in which the patient cycles between a depressed phase and a manic phase. It can be managed effectively by treatment with the drug lithium carbonate (Carbolith®). Many of the considerations mentioned above about depression apply equally to bipolar disorder. It is a sad fact that many people with this condition are reluctant to accept that they need the drug when they feel healthy, and the almost inevitable relapse when they take themselves off the drug can be extremely disturbing. Lithium does not affect people who are not manic-depressive, and has negligible addiction liability.

5.4 Schizophrenia

In this condition the individual has only transient contact with reality. The patient may become violent or be tractable the whole time, but it is clear that they do not see the world in the same way as other people. It used to be necessary to incarcerate people with this condition, but in the 1950s it was discovered that reserpine (Serpasil®) had some beneficial effects, although it also produced depression. This discovery was followed by the development of chlorpromazine (Largactil®), the founder member of a class of drugs called the phenothiazines, which include such agents as thioridizine (Mellaril®) and trifluoperazine (Stelazine®).

Another agent commonly used to treat schizophrenia is haloperidol. These drugs are effective although they do have some significant adverse effects, particularly movement disorders. More recently, some newer drugs have appeared which have a reduced incidence of severe adverse effects and which may be more effective in resolving aspects of the disease such as social withdrawal and isolation, which are seldom managed effectively by the older drugs. The agents used in this condition are shown in Table 7. None have any significant abuse liability.

TABLE 7: Antipsychotic Drugs

Phenothiazines
- Chlorpromazine (Largactil®, Thorazine®)
- Methotrimeprazine (Nozinan®)
- Promazine
- Fluphenazine (Modecate®)
- Perphenazine (Trilafon®)
- Prochlorperazine (Stemetil®) (antiemetic)
- Thioproperazine (Majeptil®)
- Trifluoperazine (Stelazine®)
- Mesoridazine (Serentil®)
- Pericyazine (Neuleptil®)
- Pipotiazine (Piportil L4®)
- Thioridazine (Mellaril®)
- Olanzapine (Zyprexa®)

Thioxanthines
- Flupenthixol (Fluanxol®)
- Thiothixine (Navane®)
- Zuclopenthixol (Clopixol®)

Butyrophenones
- Haloperidol

Others
- Quetiapine (Seroquel®)
- Risperidone (Risperdal®)
- Clozapine (Clozaril®)
- Loxapine (Loxapax®)
- Pimozide (Orap®)

5.4 Medication to Combat Addiction

The idea that substance use disorder is primarily a condition of disruption of normal brain function raises the possibility that drugs can be devised that will restore normal function in addicts, who will thus lose their craving for the drug. While the concept is simple enough, we have been handicapped by the complex nature of human thought and our lack of understanding of all the factors which lead one individual to become addicted, while another who has been exposed to apparently the same stimuli, remains addiction-free. A rather hit-and-miss approach, has, however, yielded some modestly promising compounds.

Some strategies have been discussed elsewhere in this report. For example, replacement therapy, in which the addict is given a drug that is a legal analogue of the one they have been taking (such as methadone for opioid addiction). Another very familiar replacement approach to tobacco dependence is the use of the "patch" or other nicotine replacement therapy. While methadone is designed to reduce the problems associated with taking an illicit drug, nicotine replacement therapy is designed specifically to promote abstinence from smoking. Administration of controlled doses of nicotine has the effect of separating the addiction itself from the social factors associated with it; the patient learns first to deal with the situations in which smoking would normally occur without having to deal with the actual nicotine addiction. The nicotine is

tapered so that the withdrawal from the addiction is easier. This therapy substantially increases the success rate in attempts to stop smoking.

Antagonists, which theoretically prevent the individual from obtaining their desired drug experience, such as naltrexone to block the heroin experience, were also discussed previously. It is worth mentioning in passing that the use of antagonists may not always be helpful. When cocaine addicts were treated with antagonists of cocaine, at least in some cases, they merely increased the dose of cocaine until they had overcome the blockade, something that actually increases the risk of life-threatening complications. Naltrexone, however, does seem to be effective in both alcohol and opioid dependence. Disulfiram (Antabuse®) and calcium carbimide (Temposil®) used to be employed in alcohol aversion therapy, since if the person was receiving the drug and then consumed alcohol, they would become unpleasantly ill. At best, this approach worked for only a few recovering alcoholics, and both drugs have now been withdrawn.

Acamprosate (Campral®) is an agent that is effective in diminishing the craving for alcohol, but is probably not effective for opioids or cocaine, at least based on animal studies. In humans, it improves abstinence and increases time-to-next-drink, and although it is reasonably expensive, there is good European data to suggest that its use is cost-effective.[28] The mechanism of action of acamprosate remains mysterious; it seems to be a partial agonist at the NMDA receptor, which normally interacts with the transmitter glutamate, which seems to exert a modulating effect on GABA in the brain. The drug itself is actually a GABA derivative. Acamprosate is not yet available in Canada or the U.S.

There have been extensive trials of the use of other agents in decreasing craving and promoting abstinence from alcohol and other drugs in both humans and animals. Lithium, which is used for bipolar disorder, and the antidepressants seem to have no significant effects in humans. Some animal data suggested that a modest reduction in drinking behaviour could be achieved with the SSRI fluoxetine, but this has not been substantiated in humans.

Very recently the anti-epileptic drug topiramate (Topamax®) was tested in a short-term (12-week) trial of alcoholics who were still drinking but were interested in reducing their alcohol consumption or becoming abstinent. The drug was dramatically more successful than placebo in reducing drinking in this group, but so far there have been no follow-up data. The drug is not approved for reducing cravings for alcohol, and more data will be necessary before that can happen. There is a plethora of new drugs for seizure disorder, and they are being used experimentally in a variety of conditions from migraine to labile

[28] Rychlik, R., Siedentop, H., Pfeil, T. & Daniel, D. Cost-effectiveness of adjuvant treatment with acamprosate in maintaining abstinence in alcohol dependent patients. *European Addiction Research*, 9, 59-64.

mood, as well as in epilepsy. It remains to be seen whether the results of this trial are supported by other work, but this one trial is encouraging.[29]

This is an area that will become increasingly important, but at present we have had only limited data about reduction of craving or promotion of abstention as a result of using therapeutic drugs. A few herbal or "natural" approaches have also received attention, as described in the brief section on herbal preparations earlier in this report.

Points to Consider

- The complex nature of the condition often referred to as "dual diagnosis," in which substance use disorder and mental illness co-exist, requires a successful team approach. It is very important that the caregivers for both components of the patient's problems work closely together to provide appropriate support and therapy.
- An important role of the person(s) providing support for recovering addicts is to convince the individual and his or her friends and family that medical treatment is being provided and this is quite distinct from the previous self-administration of drugs for pleasure. The public often fails to make this distinction.
- While theoretically it might be possible to devise a drug that will reduce or abolish cravings, we are still quite a long way from using this approach routinely. Considering the multitude of personal, environmental and physiological factors that bear on the initiation and maintenance of addiction, it seems improbable that a drug to reduce craving will provide a successful resolution of the problems of addiction.

[29] Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., Javors, M.A. & Ma, J.Z. (2003). Oral topiramate for treatment of alcohol dependence: A randomized controlled trial. *Lancet, 361*, 1677-1685.

6. Drug-Drug Interactions

6.1 Overview

Drugs may interact with one another to produce unexpected results. This is an issue that the physician and pharmacist must keep in mind when a patient is taking more than one drug. Awareness of the problem helps to reduce the incidence of adverse drug interactions, but many of these are unpredictable and not manifest until a drug has been used for some time—often a matter of years. The major routes of interaction involve the ability of some agents to enhance or impair the ability of the body to eliminate a drug from the blood. If the transformation of a drug to inactive products, usually carried out by the liver, is impaired, the drug will accumulate to higher plasma concentrations and thus can create problems for the patient. Other drugs may enhance the drug-transforming activity of the liver, resulting in more rapid clearance of the drug from the blood, lower levels in the blood and therapeutic failure. This applies to therapeutic drugs, and to drugs taken for non-medical purposes.

6.2 Interactions with Alcohol

Central nervous system drugs are particularly prone to drug interactions, so combinations of recreational and medical drugs can produce problems. A good general rule is that **all drugs that affect the brain can interact unpredictably one with another.** For example, alcohol is such a drug, and combinations of alcohol with other drugs can be a particular hazard. Alcohol interacts with phencyclidine (PCP) to produce extreme loss of motor co-ordination, which may partly explain the high incidence of deaths by drowning produced by this combination. It also interacts with the stimulants to produce bizarre behaviour, sometimes violent and unpredictable, and with the antihistamines, benzodiazepines, and other sedative-hypnotic drugs, producing effects that are often those of enhanced sedation and loss of motor co-ordination. Combinations of alcohol and the benzodiazepines are potentially lethal, and the degree of impairment that this combination produces has been responsible for many traffic accidents. In a depressed patient, alcohol intoxication can result in a suicide attempt, and the combination of alcohol with a large dose of any depressant drug can turn such an attempt, which would normally result in an uneventful recovery, into a life-threatening situation.

Combinations of alcohol with antidepressants and antipsychotic drugs have not been systematically studied, but there is good reason to believe that interactions will occur, particularly with those agents which have substantial sedative properties, such as doxepin (Sinequan®) or thioridazine (Mellaril®). Risk of drug interactions are less with the SSRI antidepressants than the other major classes.

Points to Consider

- The Alberta Pharmaceutical Association now puts warning labels on bottles containing medication that may interact with alcohol. The unpredictable nature of drug–drug interactions, and particularly the interaction of mood-altering drugs with alcohol, is probably not emphasized enough, and can cause serious acute problems from misadventure to death from depression of brain function. Interactions with drugs such as marijuana or cocaine are also inevitable, but there is little reliable information in this area.

7. Special Patients

7.1 Children and Adolescents

Newborn infants behave very differently from older adults when treated with drugs, because many of the systems for handling drugs are immature. The situation slowly resolves itself over the first year of life, and in many ways children from the age of five onwards, and particularly teenagers, behave similarly to older adults when challenged with most therapeutic drugs. Adolescents, however, do represent a special case, because although the body is capable of handling drugs as well as the body of an adult, the mind of young people is developing and changing at a rapid rate. Habits and attitudes are being formed which may, later, be very difficult to change or eradicate. Recent studies using imaging techniques have shown that the brain expands rapidly at about the time of puberty, particularly in the frontal cortex, and thereafter a process of "neuronal pruning" occurs. During this stage, circuits that are deemed by the brain to be useful improve their ability to communicate, while those deemed not useful become slow or absent. There is convincing evidence that this pathway can be influenced adversely by alcohol, and it not unreasonable to suppose that any other drugs that affect mood and behaviour may cause problems.

This means that the use of drugs in adolescence needs to be considered with particular care. If the approach is that of using drugs to correct a physiological problem, and with luck, discontinuing the drug once cure has been affected, then a responsible role model is being established. If young people grow up with the idea that physical, and particularly mental discomfort, can be resolved easily and pharmacologically under all circumstances, the tendency to use drugs for recreational purposes will be enhanced. Convincing evidence has been presented that the use of non-medical drugs by children correlates well with the use of medical drugs by their parents.

7.2 The Elderly

The elderly are at particular risk, because they do have more illness and in consequence need more drugs. There are also changes in the body as we age which generally make us more sensitive to drugs and, in consequence, it becomes easier to overdose patients or for patients to overdose themselves. In summary, there are a variety of habits which are relatively common among the elderly and which make the risks associated with medication greater than they need to be. For example,

- sharing medication

- sequestering old medicines and re-using them without approval from a physician
- failing to follow the required dosage schedule
- taking too much or too little
- "doctor-hopping" in which the patient will covertly be seeing several different doctors and using medication prescribed by each
- combining drugs with alcohol or foodstuffs with which the drug may interact—failing to observe the warning labels
- self-medicating unnecessarily or excessively with non-prescription products
- relying on drugs to deal with problems that could better be dealt with by lifestyle changes

Some members of the medical profession are also guilty of over-medicating elderly patients, and sometimes failing to realize that the change in behaviour which is attributed to senility may actually be an adverse reaction to unnecessary medication. The elderly sometimes respond in a paradoxical way to drugs, for example, becoming more agitated when a sedative is given. This may cause the physician, who fails to recognize the problem, to increase the dose of the sedative. Equally, sleep patterns change with age, and some elderly patients receive sleeping medication in an attempt to force them into the sleep pattern of younger adults. Sometimes grief may appropriately be treated short-term with the benzodiazepines, but the prescription is sometimes continued long after the patient should have recovered, leading to an expensive and damaging dependence on these drugs.

7.3 First Nations People

A survey of First Nations communities in Canada revealed that about 40% of such communities felt that prescription drug abuse was an occasional problem, while more than one quarter saw the problem as "frequent."[11] This view was consistent between the community members, their leaders, social workers and addiction counsellors. Comparable statistics for other communities in Canada do not seem to be available, but it is unlikely that 35% of those living in such communities would see prescription drug abuse as a "frequent" or "constant" problem. A discussion of substance abuse by First Nations and other Aboriginal peoples is beyond the scope of this review, but it is important to appreciate that prescription drug abuse represents a significant problem in this segment of Canadian society. While prescription drug use may be less of a problem than alcohol (almost half the communities noted in the survey above saw alcohol

[11] National Native Alcohol and Drug Abuse Program (NNADAP) general review: Health service workers questionnaire (accessed online at: http://www.hc-sc.gc.ca/fnihb-dgspni/fnihb-cp/nnadap/publications/nnadap_questionnaire.pdf).

abuse as a "constant problem"), it is certainly a serious issue, and Aboriginal leaders claim that several deaths each year are due to prescription drug abuse.[31]

7.4 The Mentally Ill

Alcohol may play a role in depression in some patients, as may other sedatives. The benzodiazepines are not useful in depression, but they are sometimes prescribed as a result of misdiagnosis. Equally, as mentioned above, medication for mental illness may interact with drugs of abuse. It is generally true that patients with mental illness have greater difficulty dealing with recreational drugs, and will do best if they restrict their drug use to prescribed medication.

7.5 The Chronically Ill

This group of patients may be seriously or terminally ill and will need pain relief from opioids as well as other medication. Usually, addiction is not an issue. A different group are those who might be characterized as "chronically unwell." These people often suffer from real and sometimes painful conditions such as fibrositis that are often not managed successfully with drugs. These individuals are in genuine distress, and will often spend a great deal of time visiting different doctors in an effort to obtain relief. Sometimes, in a sincere but misguided effort to help, the doctor may prescribe unnecessary medication, and these patients often end up taking a drug for anxiety, which may lead to a second problem of dependence. These individuals often need care, affection, support and friendship more than they need drug therapy, and may better be dealt with through social agencies than pharmacological ones.

7.6 The Pregnant Patient and the New Mother (and women in general)

Taking any drug during pregnancy may result in medication of the developing fetus. Most therapeutic drugs cross the placenta and reach the fetus, although fortunately many do not appear to do any harm when they are there. There is a critical stage during gestation, usually defined as from the third week to the third month after conception, where the fetus is particularly at risk of being subject to birth defects. All drugs that affect the brain get into the fetus, and this means that consumption of recreational drugs during pregnancy (and particularly during the critical stage) is not a good idea. This does not mean that useful supplements such as iron or folate, or therapeutic drugs needed by the mother should be prohibited, but it does represent a time when all ingested substances must be taken with caution. The issue of fetal alcohol spectrum disorder (FASD) does not belong in this report, but it is a real and ongoing

[31] C-Health, June 2001 (accessed online at: http://www.canoe.ca/Health0106/06_health-cp.html).

concern. Women who follow these precautions will minimize the risk of fetal damage:

- If you may be pregnant, tell your doctor at once.
- Avoid any non-prescription medication during pregnancy unless it is specifically recommended by your doctor.
- Avoid recreational drug use during pregnancy (including alcohol and tobacco).
- If you are pregnant, follow your doctor's instructions about medication exactly.
- Some drugs (lithium is one example) are excreted in breast milk and can produce some (usually mild) effects in the newborn that is breastfed. One could thus add an additional caution: If a child is being breastfed, the doctor should realize this and provide any necessary warnings.
- It is also worth noting that prescriptions for drugs with abuse liability are written about 50% more often for women than for men, and it is likely, although not established, that this will lead to a higher incidence of medication abuse in women. Because women are joining the medical profession in increasing numbers, it is to be hoped that this sort of disparity will disappear. There is no reason to believe that women have a greater need for drugs that are liable to abuse.

7.7 The Athlete

- Drug abuse involves not only the use of damaging agents to improve athletic performance, but also the use of drugs to speed recovery from injury when such use may have harmful effects. The competitive athlete will often take excessive amounts of anti-inflammatory drugs to deal with injury rather than the classic quartet of rest, ice, compression and elevation. The anti-inflammatory drugs have significant adverse effects and the temptation to over-use them is considerable and can be considered to represent an example of drug abuse.

Points to Consider

- It is helpful if we can identify, in advance, situations that may lead to problems. Special groups of people, for very different reasons, represent populations that are particularly at risk from misuse or excessive use of prescribed drugs, and could well be targeted for specific educational materials.

8. Legal Controls

8.1 Overview

Federal legislation controlling substances liable to abuse is enshrined in the *Food and Drugs Act*[32] and the *Controlled Drugs and Substances Act*.[33] These acts deal comprehensively with food, legal and illegal drugs, cosmetics and devices. Schedule I of the *Controlled Drugs and Substances Act* covers the opioids, Schedule II covers cannabis, and Schedule III covers other agents including stimulants and hallucinogens. The range of possible penalties suggests that the severity of the sentence may differ dramatically from courtroom to courtroom. The current dispute about the medical use of cannabis also suggests that the legislation still needs substantial work.

The overall philosophy of legal controls actually differs widely from country to country, depending on whether a pragmatic or a moralistic view is adopted. The addict may require $100 a day or more to support an opioid dependency, and the money almost invariable comes from illegal activities, and is distributed to those engaged in another illegal activity—dealing in illicit drugs. The losses incurred to society through crime and the costs of necessary law enforcement can easily total $100,000 a year per addict. Most legislation has been designed on the reasonable basis that the social effects of drug addiction are sufficiently detrimental to warrant stringent penalties against the non-medical use of the agents. Unfortunately, these controls seem to have achieved little in the reduction of the incidence of addiction, but do ensure an increase in the profit margin of the drug dealers: whatever is scarce becomes expensive. In Malaysia, trafficking in drugs carries the death penalty, a fact that is announced on each arriving international flight. Despite this approach, there is still a significant problem in Malaysia; the risks are high, but to some individuals the potential profits are worth it. Indeed, in some countries, importing codeine-containing analgesics for personal use is potentially a problem. The approach of attempting to control illicit drugs by stringent legislation can obviously have an impact on the appropriate use of drugs for illness.

The alternative is to have a laissez-faire attitude, but this is also fraught with difficulties. The public is reluctant to permit recreational drug use to go unpunished, and would be equally unhappy with a system that allowed medication to be freely available without the need for prescription. Indeed, there is an entirely rational move to require herbal and similar products to show proof of efficacy and safety comparable to those of drugs, if therapeutic claims are being made. In addition, of course, it would be irrational to have a system

[32] *Food and Drugs Act*, Revised Statutes of Canada 1985, c. F-27, s.1.

[33] *Controlled Drugs and Substances Act*, Revised Statutes of Canada 1996, c. 19.

where one could sell a chemical on the streets as an intoxicant without penalty, but one could not legally sell the same compound in a pharmacy. The resolution of these difficulties is not easy, and the fact that it will probably be attempted by those who have a political background, but no knowledge of either pharmacology or substance use disorder, is far from reassuring.

8.2 Cannabis

The issue has become important for Canadians because of proposed changes that would result in the decriminalization of cannabis. Already we have problems with the regulations concerning use of this drug for medical or quasi-medical purposes. The original government proposal (Bill C-38) was to decriminalize possession of small amounts of cannabis (less than 15 g) but increase the penalties for trafficking or growing marijuana. It seems likely that this would increase the demand for the drug, under circumstances where production was attended by increased risk of arrest or imprisonment, a situation that might reasonably be expected to enhance the profits of the "grow-ops." A slightly more rational alternative might be to permit cultivation of small amounts of the drug to be decriminalized and for cultivation to become legal for those who have permission to use the drug for medical purposes. This would diminish the risk of adulteration (there are anecdotal reports of marijuana being deliberately contaminated with methamphetamine or other noxious compounds), provide a source of marijuana for medical use and go some way to reduce the profits of the illegal mass cultivation of cannabis by organized crime. Passage of the federal legislation to decriminalize cannabis was stalled in the House of Commons and the Bill died on the order paper when parliament was dissolved (May 2004). It remains to be seen what, if anything, a new Canadian government will do to further cannabis legislation and medical regulation.

9. Drug Advertising

9.1 Overview

A very considerable amount of money is spent advertising non-prescription medication to the general public and prescription medication to physicians. That the money could be better spent on research is unquestionable, but under the present system, some advertising is inevitable. The pharmaceutical industry polices itself in this regard, and the calibre and ethics of the advertising business for pharmaceuticals is probably higher than in any other industry. This does not mean that all the advertisements are either tasteful or appropriate, and implications are sometimes made, particularly for non-prescription medication, which would be hard to substantiate scientifically. This could, of course, be controlled by constructing a bureau to screen all drug advertisements, but the gain in bureaucracy and cost would probably not be paralleled by a corresponding improvement in sensible use of medication.

A relatively new development in the United States has been the direct marketing of prescription medication to the general public ("Ask your doctor about..."). This results in increased pressure on the physician to prescribe and a considerable loss of physician time while he or she explains to the patient *why* this particular medication is not indicated. No doubt it also results in enhanced profits for the pharmaceutical companies. Although a significant number of Canadians watch U.S. television, and are thus exposed to this approach, we should use all reasonable efforts to ensure that similar marketing of prescription drugs to the public does not happen in Canada.

9.2 Internet Pharmacies

An even more egregious nuisance has been the profusion of online pharmacies that market prescription medication via the Internet. Quite apart from the insufferable proliferation of "spam" e-mails, the concept of prescription medication becoming available to those who have not been seen by a physician or other health professional is very disturbing. It is uncertain who would be legally responsible if someone purchased and used an agent by this means and became seriously ill from a predictable drug reaction or interaction. I suspect that the physician who signed a prescription without seeing the patient would bear the brunt of the claim—and rightly so.

10. Concluding Remarks

The issue of medications associated with substance abuse is complex, but it is worth bearing in mind that the body makes no distinction about the purpose for which a drug is consumed. Both substances taken for pleasure and medications designed to treat disease are subject to the same sort of processes of absorption, distribution and elimination, and share many of the same mechanisms in the alteration of physical or mental function. As outlined in Sections 2 and 3, many of the same drugs that are used by addicts also have a major role in the management of disease. This helps to emphasize that addiction involves a great deal more than merely consumption of psychoactive drugs over a long period of time, and this observation bears on the use of psychoactive drugs for the treatment of disease in the addict population, which was discussed in Section 5.

There are some practical consequences of the material in this report. First, those working with addicts or with patients taking drugs liable to abuse need to focus clearly on the motivation for consumption of the drug. If there is an ongoing need for medication to manage a particular condition, this is not an addiction, even though the drug might be liable to abuse. All too often, what starts out as a reasonable therapeutic use of the drug can turn into an addiction, because the condition has disappeared but drug use continues. This is a subtle distinction, but it is necessary for those who work in the addictions field to distinguish clearly between, say, long-term use of an antidepressant in a depressed patient, and long-term use of benzodiazepines in a patient where the need for the drug is no longer present. The former is not drug abuse, but necessary and possibly life-saving therapy, while the latter may represent an addiction.

Second, it is appropriate for counsellors and others to have at least some understanding of the pharmacology of the drugs involved, whether they are illicit drugs like marijuana, legal non-medical drugs like alcohol, or drugs used to treat disease. An understanding of why a particular patient is taking the drug(s) in question and what drug effects can be anticipated may be invaluable information in treatment of an addicted patient.

Third, prevention of addiction depends in part on an informed team approach to disseminating information. There is often a surprising lack of knowledge about addiction on the part of physicians, and an equivalent lack of knowledge about medication on the part of those who work in social service agencies. This may be inevitable, but an open and informed dialogue between all the groups for whom the issue of drug addiction is a concern, can minimize the problems.

Fourth, addiction to medically useful drugs is an ever-present reality, and treatment may be as necessary as it is with alcohol dependence. Involvement of the physician in the process of treatment is essential, and may require considerable tact and flexibility on the part of the counsellor or treatment centre.

Finally, those knowledgeable about addiction should become involved in the development of legislation relevant to drugs with abuse liability, so that misinformed public opinion does not carry as much weight.

This report is a brief overview with many omissions. Any of the issues raised could be developed into a much more extensive and balanced review. Equally, the area is itself controversial, and a different author might have reached different conclusions. Nevertheless, it does provide some insights into the nature of the interaction between medical drugs and addicting drugs, and may stimulate further interest in this subject.

11. Additional Reading

In attempting to suggest additional material, I have not included journal articles from the medical literature. These form the basis of our knowledge about medication and the addictions, but they are not usually accessible or intelligible except to those with medical training. The volumes listed are those which will provide answers to specific questions about medications, and should be considered for purchase by the libraries of agencies, or even of individuals, who work with drugs and drug-using patients.

"The Pharmacological Basis of Therapeutics," Eds: Hardman, J. C. G., Gilman, A. and Limbird L. L. 10th Edition, 2001, McGraw-Hill, New York. *This is the "Gold Standard" of Pharmacology texts. The book is massive and sometimes difficult reading, but contains almost anything that one might wish to know. A good medical dictionary may be necessary to interpret the articles.*

"Human Pharmacology—Molecular to Clinical," Eds: Wingard, L. B., Brody, T. M., Larner, J. and Schwarz A. 3rd Edition, 1998, Mosby Year Book, St. Louis. *A very impressive new book, similar to the text noted above, but more readable and with more illustrations. A new edition is badly needed.*

"Uppers, Downers, All Arounders: Physical and Mental Effects of Psychoactive Drugs," Inaba, D. S. & Cohen, W. E., 4th Edition, 2000, CNS Productions, Ashland, Oregon. *An excellent and sensibly written book, with the health professional in mind, but not full of dense technical language.*

"Compendium of Pharmaceuticals and Specialties" (CPS), 2004, Canadian Pharmacists Association, Ottawa. *Complete and exhaustive reference book to all agents currently available in Canada. The book is based mostly on information supplied by the manufacturer, and so it cannot be described as a truly unbiased source. In addition, it is sometimes difficult to separate the critical information from the massive amount of data supplied. On the other hand, it will answer most basic questions about specific agents. Again a medical dictionary may be helpful for the non-specialist.*

"Martindales's Extra Pharmacopoeia," 31st Edition, 1996, The Pharmaceutical Press, London. *The complete reference text on all medications, worldwide. A useful reference book, particularly for dealing with unusual drugs or drugs which are not available in Canada. No new edition has appeared for eight years, however, and this may become extinct as a source of information.*

"Patient self-care," 2002, Canadian Pharmacists Association, Ottawa. *This is the equivalent of "CPS" but for non-prescription products. It contains lots of reference information and is a lot more readable than CPS.*

Brochures available from AADAC. There are a variety of brochures and fact sheets available from AADAC on licit and illicit drugs. They are uniformly clear, well written and accurate.

"Medline" or "PubMed" at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi. *This is a website from the National Library of Medicine that has a built-in search engine that will direct you rapidly to the latest scientific papers on anything to do with medicine. You may need a medical dictionary to help with the search results. You do not usually have access to the full paper, but you do receive a full reference and usually an abstract. This is an invaluable site, but you may have to use it a couple of times to get the full value from it.*

"The Vaults of Erowid" at http://www.erowid.org. *This is primarily a site for users of illicit drugs, but it contains some relevant material, and overall provides an extraordinary amount of information, anecdote, chemistry and source material. Provided you remember that anecdote is just that, you may find this site provides a different perspective that can sometimes be quite enlightening.*

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